

ANNALS OF INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

VOL. 38 (O.S., Vol. XLIII)

JUNE, 1953

NUMBER 6

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PUBL. JUNE 1952

The Unipolar Electrocardiogram

A CLINICAL INTERPRETATION

BY

Joseph M. Barker, M.D., F.A.C.P.

Cardiologist, Yater Clinic; Associate Professor of Clinical Medicine, Georgetown University School of Medicine; Director of the Heart Station and Visiting Physician, Georgetown University Hospital; Chief of Cardiology, Gallinger Municipal Hospital; Consulting Cardiologist, Arlington Hospital, Arlington, Virginia.

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Joseph J. Wallace, M.D.

Foreword By

Frank N. Wilson, M.D.

Advised By

Wallace M. Yater, M.D.

Extracts from the Reviews

The Journal of the American Medical Association, Sept. 20, 1952

Recently, many monographs on unipolar electrocardiography, with little or no consideration of the arrhythmias, have appeared and an almost "indigestible" literature has developed.

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Material on the arrhythmias and miscellaneous conditions occupy 193 pages. A select bibliography and a good index are included. The format and illustrations are good.

The persistent student or clinician will find the information necessary for the intelligent and dependable interpretation of electrocardiograms in this comprehensive presentation.

Archives of Internal Medicine, Nov. 1952

This book answers a real need for an up-to-date presentation which, starting from "first principles," covers the theoretical and practical aspects of electrocardiography in a systematic, but not encyclopedic, manner.

Texas State Journal of Medicine, Oct. 1952

It is outstanding in its field and should surely be included in the library of every internist and electrocardiographer, even the most experienced.

Medical Annals of the District of Columbia, Oct. 1952

The author, one of Dr. Wilson's pupils, has presented a difficult subject in a very clear, logical and scientific manner.

An outstanding feature of the book is the large number of diagrams illustrating and clarifying the text material in a fashion which the reviewer feels is not equaled by other books on this subject. In addition to the basic discussion on theory, the chapters dealing with Bundle Branch Block, Myocardial Infarction, Transient Myocardial Ischemia and Injury, and Ventricular Hypertrophy are especially good. Electrocardiograms illustrating the various points are ample with clear reproduction.

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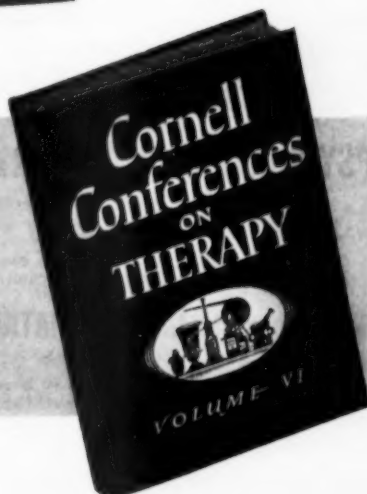
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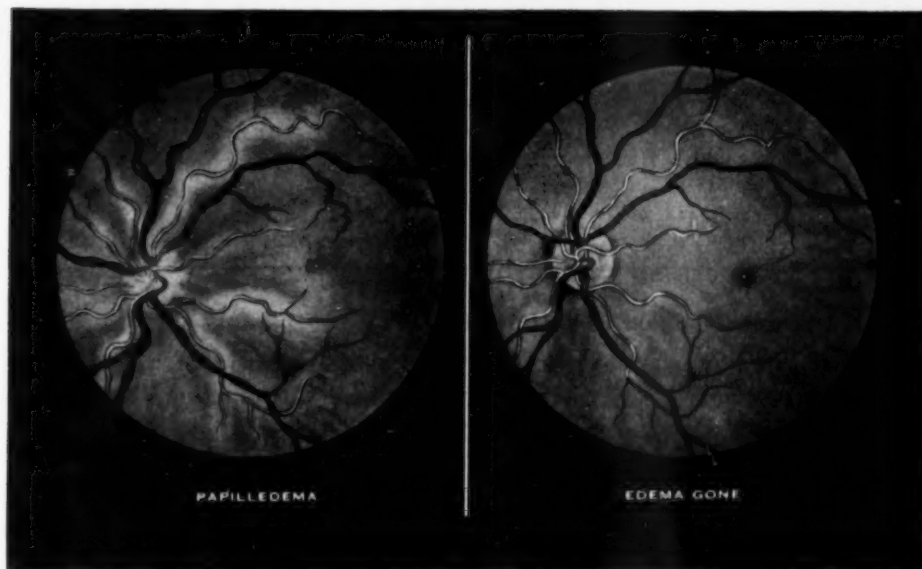
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1. Grimson, K. S.; Orgain, E. S.; Rowe, C. R., and Sieber, H. A.: J.A.M.A. 149:215 (May 17) 1952.
2. Paton, W. D. M., and Zaimis, E. J.: Pharm. Reviews 4:219 (Sept.) 1952.

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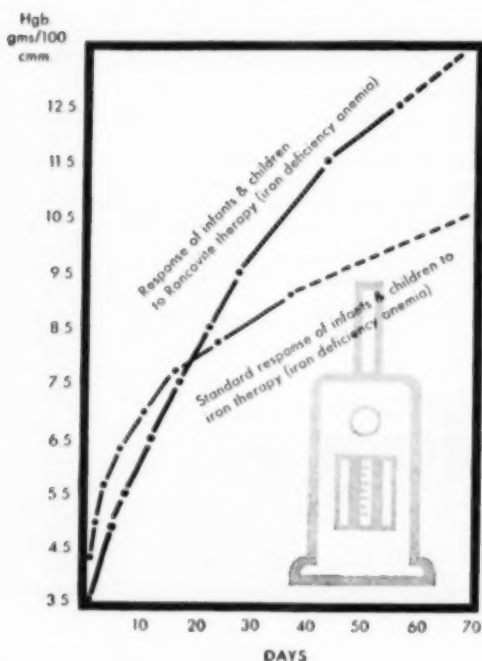
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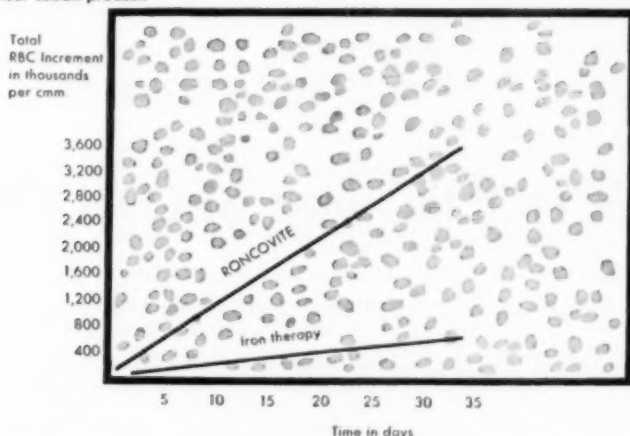
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1. Wolff, H., Med. Monatsschr. 5:239 (1951); (2) Rohn, R.J., and Bond, W.H.: to be published; (3) Berk, W., et al: New England J.M. 240:754 (May) 1949; (4) Robinson, J.C., et al: New England J.M. 240:749 (May) 1949; (5) Weissbecker, W., and Maurer, R.: Klin. Woch. 24:855 (1947); (6) Wolff, H., and Barthel, S.: Munch. M. Wschr. 93:467 (1951); (7) Gardner, F.H.: J. Lab. & Clin. M. 41:56 (Jan.) 1953.

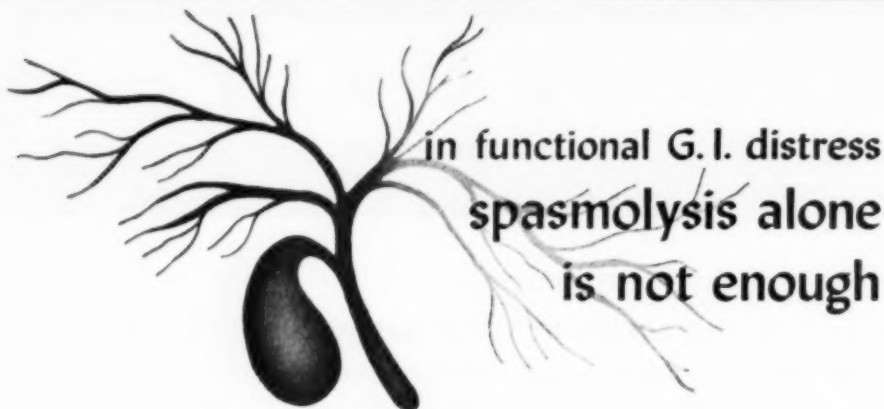
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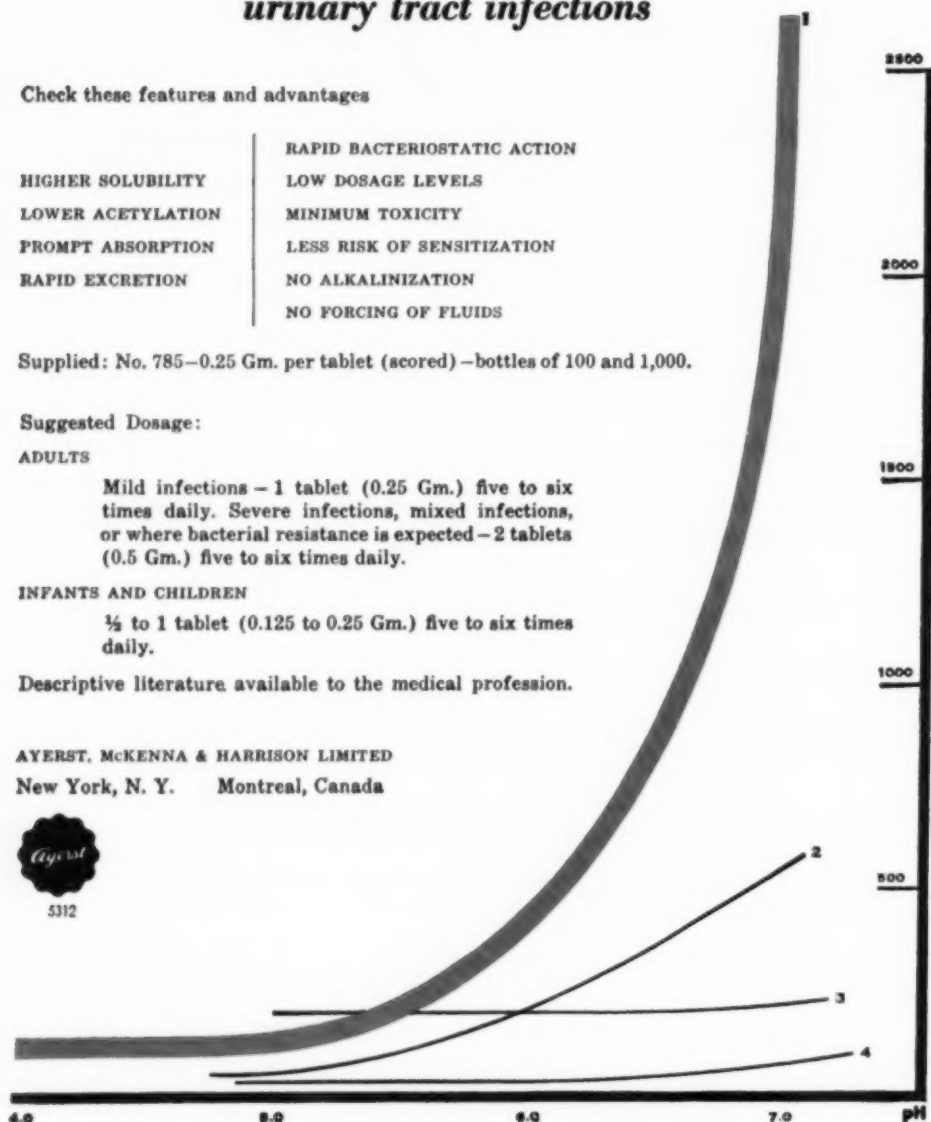
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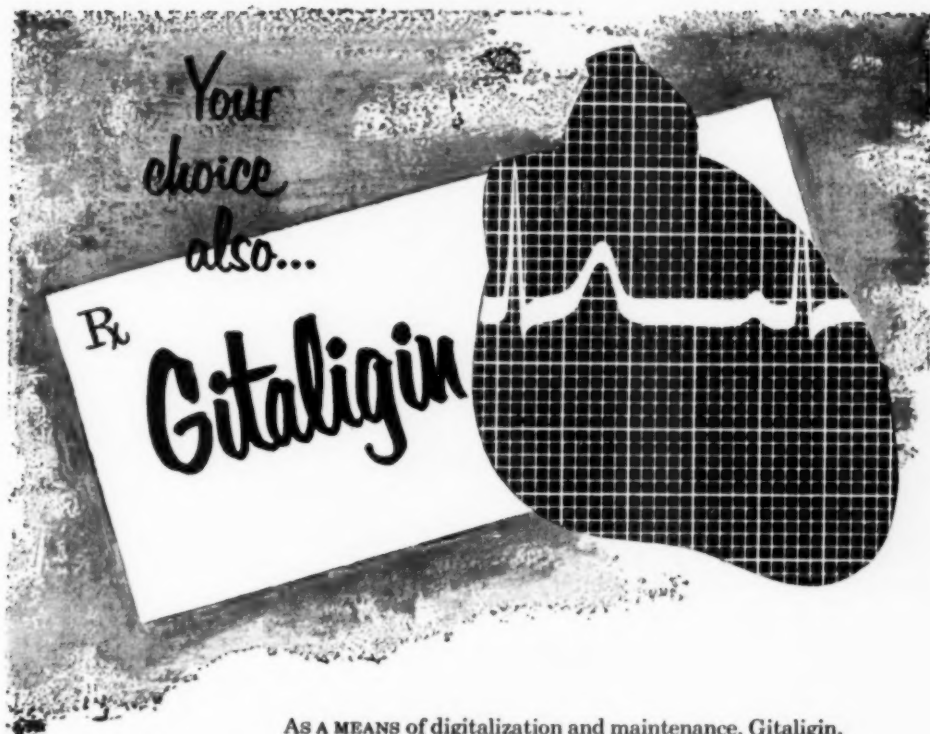
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1. Batterman, R. C.; DeGraff, A. C.; Gutner, I. B.; Rose, O. A., and Howes, J.: Studies with Gitalin (amorphous) for the Treatment of Patients with Congestive Heart Failure, *Am. Heart J.* **42**:292-307 (Aug.) 1951.

2. Batterman, R. C.; DeGraff, A. C., and Rose, O. A.: The Therapeutic Range of Gitalin (amorphous) Compared with other Digitalis Preparations, *Circulation* **5**:201-207 (Feb.) 1952.

3. Nalefski, L.: Personal Communication

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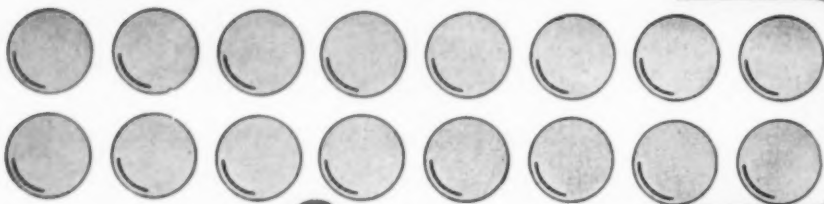
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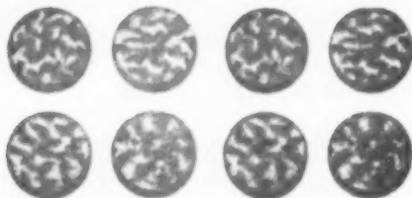
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Accumulated experience in many thousands of cases has now proved conclusively that BUTAZOLIDIN produces therapeutic results in arthritis comparable to those obtainable with cortisone or ACTH. At the same time it has become equally evident that like other potent pharmacodynamic agents BUTAZOLIDIN can cause toxic as well as therapeutic response. In general, the drug has been found to produce minor reactions in a considerable percentage of cases and serious reactions in a few. To a considerable extent such reactions are preventable by proper precautions, and when not preventable are often readily controllable. For this reason physicians are urged to familiarize themselves thoroughly with the properties and proper usage of this potent new agent before prescribing it.

not a simple analgesic

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BUTAZOLIDIN produces both improvement of function and relief of pain. In rheumatoid arthritis a recent report¹ indicates "major improvement" in 40 of 68 cases. Another notes "marked decrease in swelling, increase in range of motion, and increase in strength" in 41 per cent of patients with lesser improvement in an additional nine per cent.² A third study³ records "appreciable pain relief" in 69 per cent of patients with 50 per cent showing objective evidence of improvement. Similar favorable results have been recorded in gout, spondylitis, osteoarthritis, bursitis, and other painful musculoskeletal disorders. These findings illustrate that BUTAZOLIDIN when properly used provides gratifying therapeutic benefit in a wide variety of painful and disabling disorders.

(1) Kuweli, W. C., and Schaffersick, R. W.: *California Med.* 77:319, 1952. (2) Stephens, C. A. L., Jr., and others: *J.A.M.A.* 150:1084 (Nov. 15) 1952. (3) Steinbocker, O., and others: *J.A.M.A.* 150:1087 (Nov. 15) 1952.



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Milibis and Aralen, trademarks reg. U. S. & Canada, brand of bismuth glycolylarsenilate and chloroquine, respectively.

1. Lindsay, A. E., Gossard, W. H., and Chapman, J. S.: *Dis. Chest*, 20:333, Nov., 1951.
2. Conan, H. J., Jr.: *Am. Jour. Med.*, 6:309, Mar., 1949.
3. Emmett, J.: *J.A.M.A.*, 141:22, Sept. 3, 1949.

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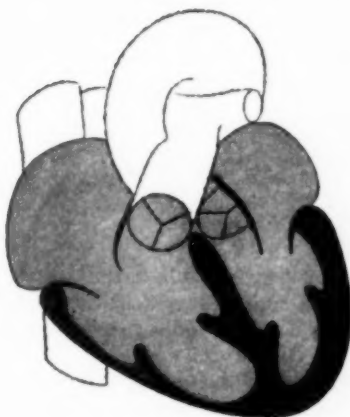
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*Strauss, V.; Simon, D. L.; Iglauer, A., and McGuire, J.: Clinical Studies of Intramuscular Injection of Digitoxin (Digitaline Nativelle) in a New Solvent. *Am. Heart J.* 44:787, 1952.

Literature and samples available on request.

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1. Rogers, M. P., and Gray, C. L.: *Am. J. Digest. Dis.* 19:180, 1952.

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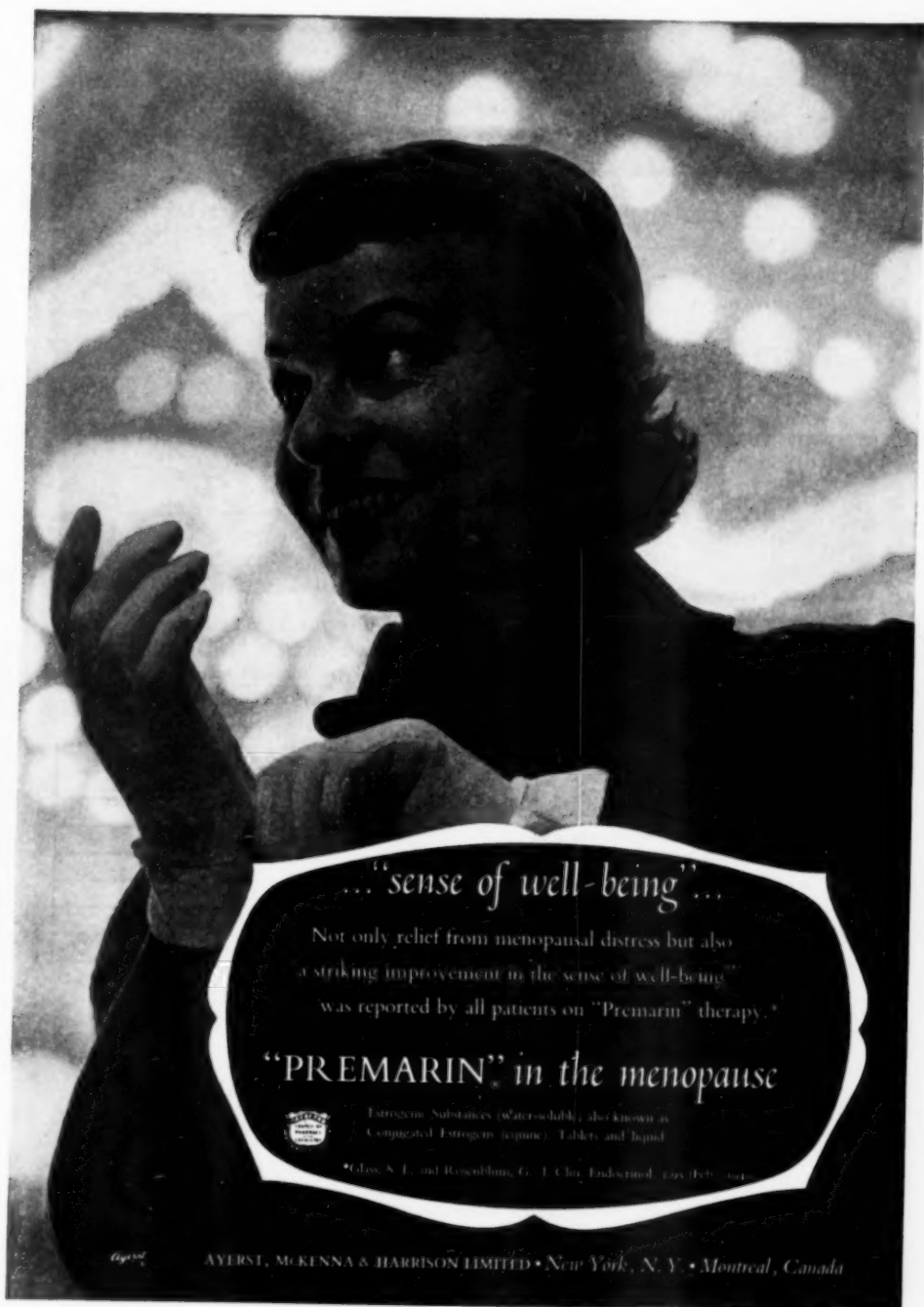
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*Clibas, S. L., and Rosenblum, G. I. Clin. Endocrinol., 1975 (Feb), 104-107.

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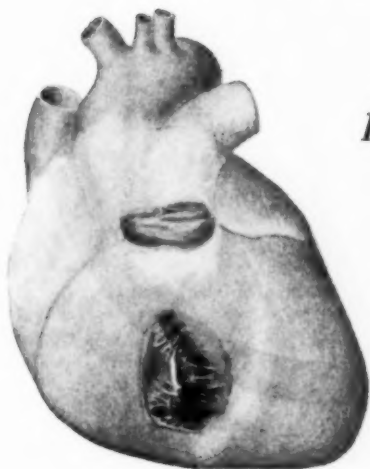
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Active research is under way to determine whether this treatment prevents development of chronic valvular disease.

Literature on Request

1. Kroop, I. G., Heffer, E. T., Turin, R. D., and Slater, S. R.: Scientific Exhibit Graduate Fortnight, New York Academy of Medicine, Oct. 6, 1952.
2. Bunim, J. J., Kuttner, A. G., Baldwin, J. S., and McEwen, C.: *J. A. M. A.* 150: 1273-1278, Nov. 29, 1952.

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1. Cutlich, L., and Opden, H. D.: J. So. Med. Assn., 43: 642, 1950



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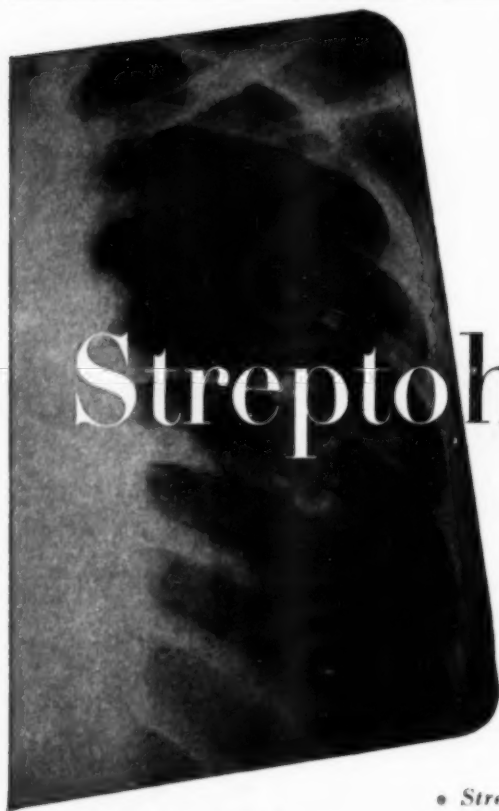
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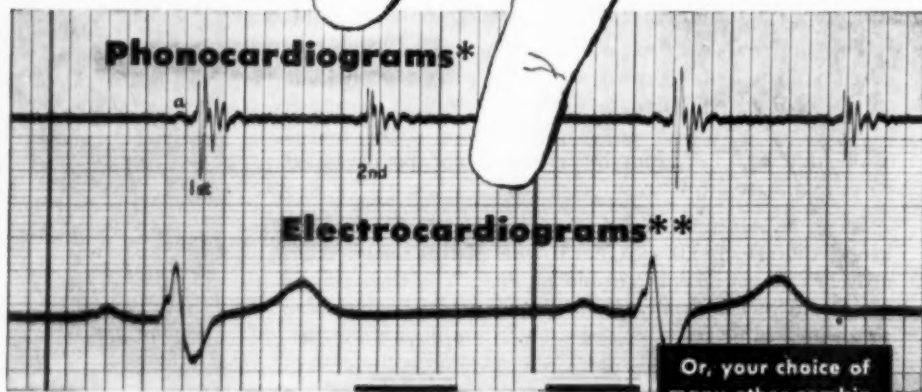
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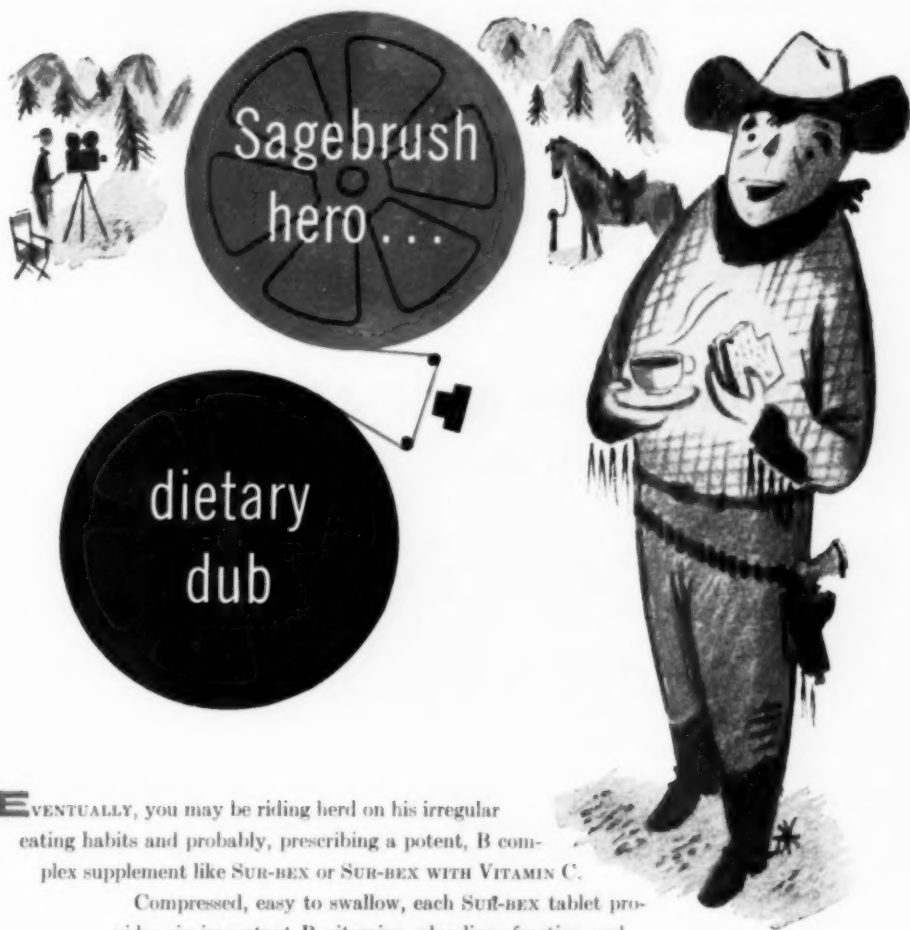
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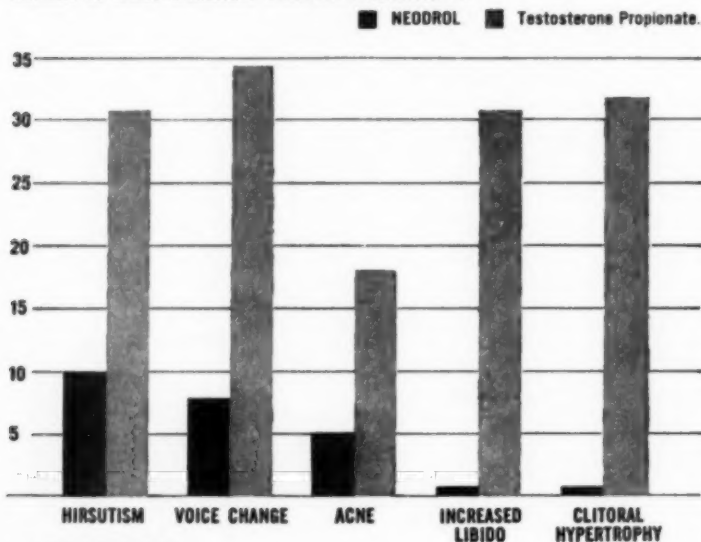
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 All patients observed for 90 days or more.

1. Escher, G. C.; Farrow, J. H., et al.: A study of forty-two cases of advanced mammary carcinoma treated with Androstano-1-one (Stanolone) therapy (Presented at American Federation for Clinical Research, Southern Section, New Orleans, La., Jan. 30, 1953). In Press.

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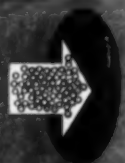


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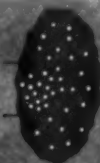
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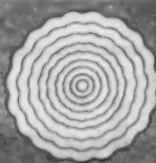
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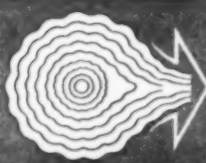
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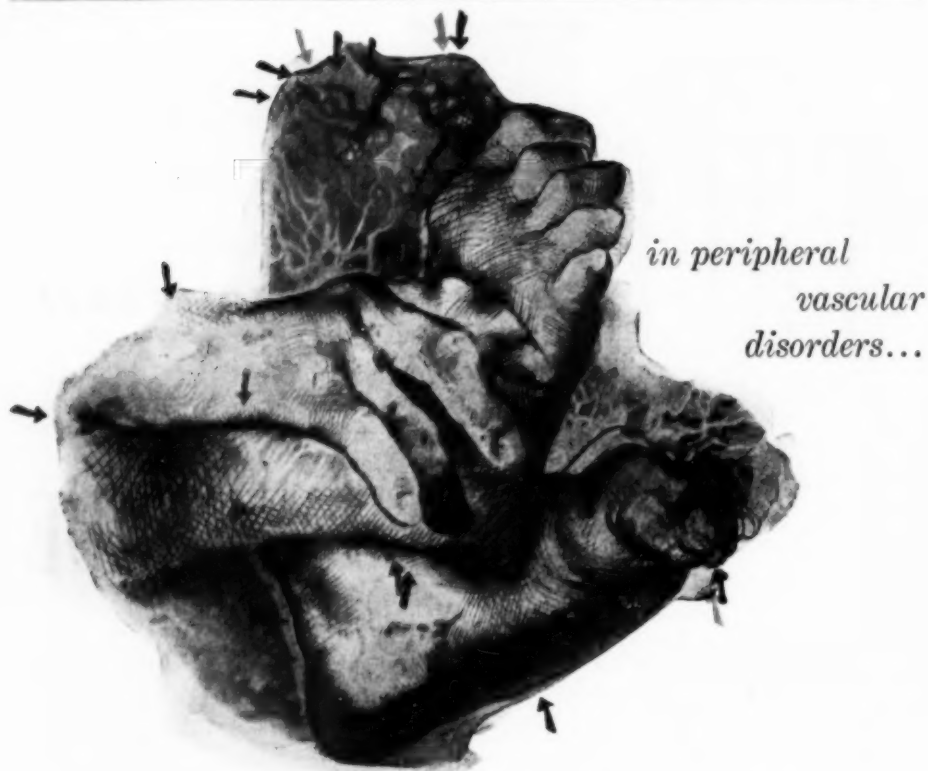
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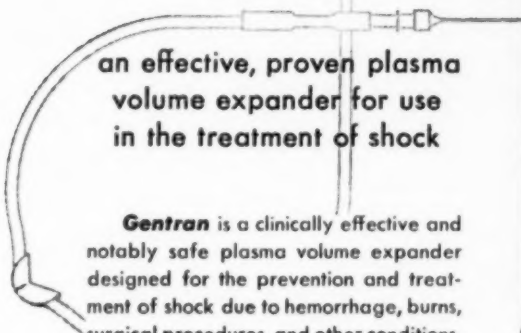
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ANNALS OF INTERNAL MEDICINE

VOLUME 38

JUNE, 1953

NUMBER 6

ADRENAL HORMONE THERAPY IN VIRAL HEPATITIS. I. THE EFFECT OF ACTH IN THE ACUTE DISEASE *

By ALFRED S. EVANS,† CAPTAIN, MC, HELMUTH SPRINZ, LT. COLONEL MC, F.A.C.P., and ROBERT S. NELSON, COLONEL, MC

THE concept that adrenal cortical hormones might be beneficial in the treatment of diseases of the liver is not a new one. Eppinger suggested their use as early as 1937,¹ but it was not until the introduction of more purified preparations and the resurgence of interest in these hormones evolving from the work of Hench and Kendall that therapeutic trials of these agents in hepatic conditions were really begun. It has now been shown in several recent reports that these compounds exert an influence on the symptomatology of *chronic* liver diseases, but that the frequency of unpleasant side effects and even of serious complications sharply limits their usefulness.²⁻⁶ The beneficial effect of adrenocorticotrophic hormone (ACTH) on certain features of *acute* viral hepatitis has been reported in five early cases studied by Colbert et al.⁷ at this hospital, and in four severe cases treated by Rifkin et al.⁸ A dramatic effect in comatose and precomatose patients with viral hepatitis has been claimed by Wildhirt⁹ in Germany, using intravenous adrenal cortical extract, choline and levulose; Ducci and Katz¹⁰ have also reported the recovery of two comatose patients with high doses of cortisone in combination with antibiotics. Encouraging preliminary results have been reported with ACTH in a controlled study of early viral hepatitis being carried out by Soborov.¹¹

The large number of patients with viral hepatitis available for study at this Center afforded an unusual opportunity to investigate more critically the possible influence of ACTH and cortisone on the course of viral hepatitis. The present paper, the first of three concerned with the results of these

* Received for publication December 2, 1952.

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studies, reports an analysis of a controlled investigation in which 20 patients with acute viral hepatitis were treated with ACTH in strict alternation with 20 similar patients receiving control injections of saline. The results are further compared with a larger group of 200 similar control patients admitted just prior to the present study.

MATERIALS AND METHODS

Plan of Study: Two groups of patients were studied in sequence. Group I consisted of 10 treated patients and 10 alternate controls who were started on ACTH or control injections in the first 10 days after onset of symptoms. Liver biopsies were done before ACTH was started and at the completion of therapy, and at similar periods in the control group. Group II consisted of 10 treated patients and 10 controls who were started on injections between the eleventh and the twentieth days after onset of symptoms. In this group no liver biopsies were done.

Criteria: (1) Uncomplicated viral hepatitis as based on typical history, physical examination, appropriate changes in liver function tests and, in Group I, confirmed by liver biopsy. It was not possible to decide on the basis of clinical or epidemiologic evidence whether individual cases had infectious or serum hepatitis. Serum hepatitis has been previously shown to be present in American soldiers admitted to this Center by experiments in human volunteers,¹² but the frequency with which these cases occur in the general run of hepatitis patients is unknown.

(2) A total serum bilirubin of 5 mg. per cent or higher prior to therapy or control injections. Every effort was made to select only cases with a rising serum bilirubin, but this was not always possible due to limitations of time and patient material.

(3) Voluntary consent for liver biopsy in Group I.

(4) Absence of contraindications to ACTH therapy.

Treatment Schedule: All patients were put at absolute bed-rest and were permitted to use only a bedside commode. A 4,200 calorie, low salt diet of 607 gm. of carbohydrate, 190 gm. of protein and 114 gm. of fat was given. Potassium acetate was administered in dosage of 2 to 5 gm. daily. Salt restriction and potassium acetate administration were discontinued at the completion of ACTH or control injections. ACTH* was given every six hours intramuscularly for the following periods: to six patients for 21 days, to 13 patients for 28 days, and to one patient for 39 days. The general dosage plan for ACTH was as follows: first and second days, 100 mg.; third and fourth days, 80 mg.; fifth through fourteenth days, 60 mg.; fifteenth through twenty-first days, 40 mg.; twenty-second through twenty-fifth days, 30 mg.; twenty-sixth through twenty-eighth days, 20 mg. All patients treated with ACTH in Group II were on this 28 day schedule. Control patients received saline in similar amounts and at similar times from a

* ACTH, Armour Laboratories. Potency in terms of LA-1-A standard.

washed and sterilized ACTH vial. Each patient had his name on his bottle and was required to identify it as his before each injection.

Observations: Clinical observations were recorded daily on a standard form. The following determinations were done at least daily: blood pressure, weight, intake-output, measurement of abdominal girth, and examination for sugar in urine. Total and one-minute serum bilirubin determinations were done at least three times a week; absolute eosinophil counts taken four hours after the 4 a.m. injection of ACTH or of saline were carried out six times a week on Group I and three times a week on Group II. The following determinations were done weekly: thymol turbidity, cephalin cholesterol flocculation, alkaline phosphatase, cholesterol and esters, zinc sulfate turbidity ("gamma globulin"), total protein with A/G ratio, complete blood count, sedimentation rate, complete urinalysis and fasting blood sugar. Bromsulfalein retention (5 mg./kg.) at 45 minutes was determined weekly after disappearance of the jaundice. Heterophil antibody titer was carried out in the first and third weeks of hospitalization. Electrocardiograms were done weekly in Group I and less often in Group II. A full-face picture was taken at start of therapy and again if rounding of the face was suggested. The patients remained in the hospital for an average of ± 75 days and were then sent to a Reconditioning Center for three weeks.

Control Patients: Patients who fulfilled the criteria for the study were alternately assigned to the ACTH or the control group, according to the date and hour of admission. The two groups received precisely the same treatment and laboratory observations; only one doctor knew which were the treated and which were the control patients. This group of control patients will be referred to as the "alternate controls" in this paper. A second group of 200 patients who were admitted to this Center in the year and one-half immediately preceding this study and who fulfilled the criteria of patients on the study program were selected for further comparison with the ACTH group and are designated in this paper as the "prior control group." One hundred of these patients were admitted in the first 10 days of illness and 100 in the second 10 days of illness. Patients treated previously with aureomycin, terramycin or chloromycetin were not included in these groups.¹³ The prior control patients received a diet similar to the study patients except that salt was not restricted; bed-rest with latrine privileges was permitted, and laboratory studies were done weekly.

The term "days on ACTH program" as used in this paper refers to completed days. Thus, day 0 represents 0 to 24 hours on treatment program, day 1 represents 25 to 48 hours, etc.

Pathologic Studies: Liver biopsies were obtained from the 10 treated patients of Group I at the beginning and at the end of ACTH administration, and at a similar time interval in the 10 control patients of this group. No complications from the biopsies were encountered. Tissue was fixed in Carnoy's solution, cut at about 5 micra and stained by the following technics:

hematoxylin and eosin, Masson's trichrome, the Romeis modification of the Bauer-Feulgen method for glycogen, and Gomori's modification of Bielschowsky's stain for reticulum. All sections were studied by one of us (H. S.) as unknowns. In addition to the usual descriptive report of each specimen, an attempt was made to quantitate the severity of certain pathologic features in each biopsy in order that the ACTH and control patients could be compared in some numerical fashion. The range of abnormality was arbitrarily graded from 0 to 3 plus for the purpose of this study. It is emphasized that this grading is peculiar to this investigation and is not meant to imply absolute values. For example, fibrosis graded as 3 plus does not

TABLE I
Pretreatment Data for ACTH and Control Patients

Test		Group						Average		
		I (1-10 days)			II (11-20 days)					
		ACTH	Control		ACTH	Control		ACTH	Control	
			Alterna.	Prior		Alterna.	Prior		Alterna.	Prior
Number of patients		10	10	100	10	10	100	20	20	200
Age		22.7	22.2	23.3	22.9	22.5	24.1	22.8	22.3	23.7
Day of disease*		7.5	7.8	7.7	14.6	13.9	14.0	11.0	10.8	10.8
Total serum bili- rubin	mg. %	8.9	7.7	8.4	10.9	9.6	9.1	9.9	8.6	8.7
1' Serum bilirubin	mg. %	4.5	4.3	4.5	5.8	4.9	4.8	5.1	4.6	4.6
Thymol turbidity	units	10.4	12.0	10.9	11.9	12.6	11.9	11.1	12.3	11.4
Cephalin flocc.	24 hrs.	1.7	2.5	2.2	2.1	2.2	2.1	1.9	2.3	2.1
Alk. phosphatase	units	9.5	10.9	8.7	9.0	8.0	9.0	9.2	9.4	8.8
Gamma globulin	units	13.6	13.9	—	14.0	15.2	—	13.8	14.5	—
Chol. esters	%	36.5	42.1	—	44.4	35.2	—	40.4	38.6	—

— Indicates sufficient data not available.

* Day of disease indicates day when ACTH and alternate controls were started on injections, and day of admission laboratory studies for prior control group.

indicate pathologic change even remotely resembling that of cirrhosis of the liver.

COMPARISON OF PRETREATMENT STATUS

The clinical and laboratory features of the treated and alternate control patients of both Group I and Group II immediately prior to the start of ACTH or control injections are shown in table I, as are similar admission studies on 200 prior control patients. It will be observed that the pretreatment status of patients receiving ACTH was very similar to the control groups in every respect, with the possible exception that the average total serum bilirubin was a little over 1 mg. per cent higher in the treated than in the control groups.

The liver biopsies performed at the start of ACTH or of control in-

jections all fulfilled the requirements for the histologic diagnosis of the acute early phase of viral hepatitis, corresponding in general to those described by Keller et al.¹⁴ Some degree of histologic variation existed from case to case, but the changes fell into such narrow range that the grading of our findings on the initial biopsy showed no real differences in the two groups of patients.

RESULTS OF TREATMENT

Two important objective criteria of improvement used at this Center are the disappearance of jaundice (total serum bilirubin (TSB) of 1.00 mg. per

TABLE II
Results of ACTH Therapy in Acute Viral Hepatitis as Compared with Control Groups

Group	Number of Cases in Group	Day of Disease When Test Returned to Normal and Presence of Statistical Difference (S.D.) of ACTH Group from Control Groups*				Day of Disease When Ready for Discharge	Relapses in Group
		Total Serum Bilirubin (1.00 mg. or less)		BSP Retention (10% or less)			
		Day	S.D.	Day	S.D.		
I (1st 10 days of illness)							
ACTH	10	53.2		71.5		92.4	4
Alternate control	10	40.4	No	55.1	No	71.8	0
Prior control	100	45.3	No	53.7	Yes	N.C.	0
II (2nd 10 days of illness)							
ACTH	10	44.1		55.0		63.2	0
Alternate control	10	55.1	Yes	57.3	No	70.0	0
Prior control	100	55.1	Yes	59.4	No	N.C.	0
Average of I and II							
ACTH	20	48.6		63.2		77.8	4
Alternate control	20	47.7		56.2		70.9	0
Prior control	200	50.2		56.5		—	0

BSP—Bromsulphalein excretion. N.C.—Not calculated.

* Presence of statistical difference indicates whether ACTH group differed significantly from either control group. This was computed by a T test to indicate statistical significance at the 5% level.

cent or less), and the decrease of bromsulphalein retention (BSP) to 10 per cent or under. When these points are reached and the liver is not enlarged more than one fingerbreadth and is no longer tender, the patient slowly becomes ambulant. The average day of illness on which treated and control patients fulfilled these criteria is shown in table 2, as is the statistical significance of the differences in the groups.* It is apparent that, as a whole, the 20 patients treated with ACTH took as long to reach a normal serum bilirubin as did the two control groups, and perhaps a little longer to reach a BSP retention of 10 per cent or less. Similarly, the time taken for treated

* Statistical analyses were carried out independently by Major William A. Haendiges, 98th General Hospital, and by the Statistical Section, Armed Forces Institute of Pathology, through the courtesy of Lt. Colonel C. F. Vorder Bruegge.

patients to meet our requirements for discharge to a Reconditioning Center* was somewhat longer than for the alternate control group. It was not possible to calculate similar data for the 100 prior controls.

Analysis of the results for the individual groups revealed that illness appeared to be prolonged in Group I patients who had been started on ACTH early in the disease, and that this prolongation was due primarily to the occurrence of four relapses, three accompanied by jaundice. If these relapses are omitted, the average time for the remaining six cases to return to a normal TSB and a BSP under 10 per cent are 38.5 and 63.1 days, respectively, figures quite similar to the control groups.

In contrast to the results of Group I, the patients of Group II, all of whom were started on ACTH after the tenth day of illness, reached a normal serum bilirubin an average of 11 days earlier than either control group, and this difference from the two control groups in each instance is statistically significant. However, the average time required to reach a bromsulfalein retention of 10 per cent or less was not shorter than in the control groups. This was due largely to one treated case who had an elevated bromsulfalein retention for 122 days. Exclusion of this case results in an average of 47 days for the other nine cases, which is about 10 days shorter than either control group. Furthermore, these 10 treated patients were considered ready for discharge to a Reconditioning Center one week earlier than the 10 patients who had received control injections of saline. No relapses occurred in Group II.

The results thus far given in this paper have dealt only with the general course of the disease and, as such, fail to indicate the impressive and sometimes dramatic effect of ACTH in producing in the majority of the cases an improved sense of well being, an increased and often insatiable appetite, and a prompt initial fall in serum bilirubin. These and other effects are discussed in more detail below.

EFFECT OF ACTH ON LIVER FUNCTION

Serum Bilirubin: ACTH produced a prompt, consistent and often dramatic initial fall in the total and one-minute serum bilirubin values in 18 of the 20 patients receiving this compound as compared to the average control case. The two patients who did not respond to ACTH remained refractory despite daily doses of 100 mg. intramuscularly or 20 mg. given intravenously over an eight hour period. One of these patients had a satisfactory eosinophil response, the other did not; neither showed much euphoria or increased appetite.

The average change in serum bilirubin for each of the treated groups, including the refractory cases, and for the alternate control groups is shown

* Criteria for discharge to a Reconditioning Center include the following: absence of jaundice, two consecutive bromsulfalein tests of 10 per cent or less, a non-tender liver not more than one fingerbreadth enlarged, and an asymptomatic status on ambulation.

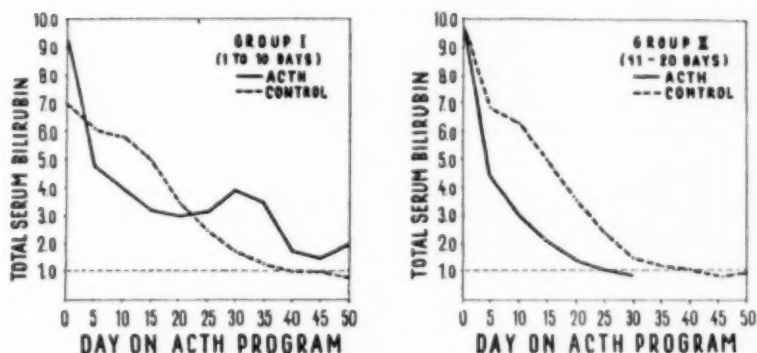


FIG. 1. Effect of ACTH on total serum bilirubin as compared with control group.

in figure 1, according to the completed days on the ACTH program. The rapid drop in both treated groups in the first five days of therapy should be noted. The secondary rise in TSB in Group I reflects the occurrence of the three relapses with jaundice, the first of which reached a peak two weeks after initiation of therapy. In Group II the TSB continued to fall toward normal, but less rapidly than during the first five days of ACTH.

This effect on serum bilirubin is presented more graphically in figure 2. Here the percentage decrease in TSB at five day intervals has been calculated taking the day injections were started as the 0 per cent baseline. The average TSB of patients receiving ACTH decreased 52 per cent after five

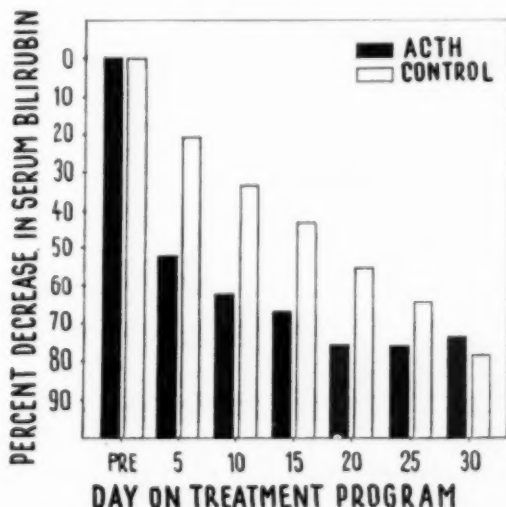


FIG. 2. Percentage drop in total serum bilirubin in 20 ACTH-treated and 20 control cases.

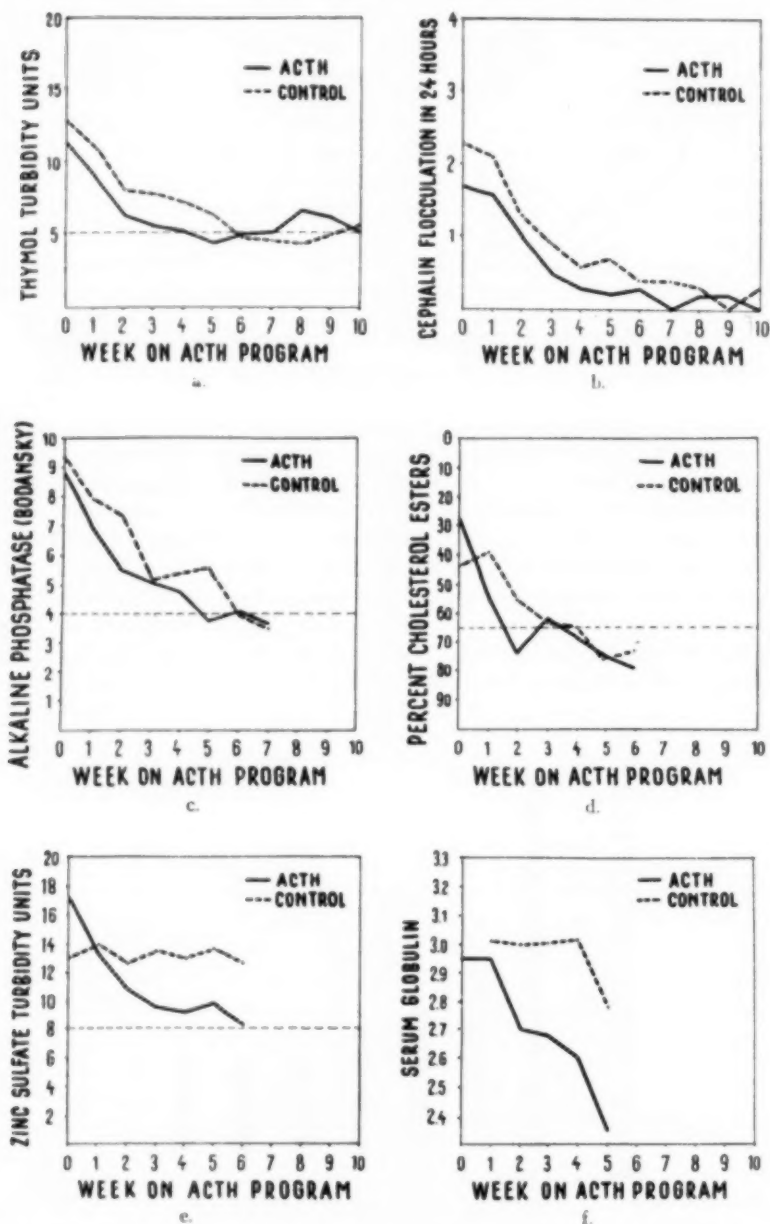


FIG. 3. Comparison of other liver function tests in 20 ACTH-treated and 20 control cases.

days of therapy, while the TSB in the control group decreased only 20 per cent during a similar period and did not in fact reach a 50 per cent decrease until more than two weeks later. The effect of ACTH on serum bilirubin was largely limited to the early period of its administration, and no further decrease was seen after 20 days' therapy, while in the control group a slower but steady decrease continued.

Flocculation Tests: The effect of ACTH on the average values for thymol turbidity and cephalin cholesterol flocculation in 20 treated cases and 20 control cases is shown in figure 3a and b. The values for these tests in treated and control patients fell in parallel fashion toward normal, and no evidence that ACTH produced a significant effect could be deduced from the data analyzed.

Alkaline Phosphatase: Initial values for both treated and control groups were about 9 Bodansky units. As shown in figure 3c, there was a slight tendency for the ACTH group to drop more rapidly during the first two weeks, the treated group having dropped 38 per cent at the two week point as compared with a 23 per cent drop in the control group.

TABLE III
Cholesterol and Esters in 20 Patients Treated with ACTH and in 20 Control Patients

Fraction	Group	Pretreatment	Week on Treatment				
			1	2	3	4	5
Total	ACTH	243	241	247	280	280	280
	Control	219	200	228	246	256	232
Esters	ACTH	71	128	197	186	191	197
	Control	95	77	127	155	167	173

Cholesterol and Esters: Cholesterol esters, expressed as per cent of total cholesterol, tended to return to normal more rapidly in the ACTH group than in the control group (figure 3d). At the two week point the treated group had an average of 73 per cent cholesterol esters, as compared with 56 per cent in the control group. Table 3 lists the results of determinations for absolute values of total cholesterol and cholesterol esters. The ester fraction and, to a lesser extent, the total cholesterol fraction were found to be depressed early in hepatitis prior to treatment, in accordance with the observations of Gardner et al.¹⁵; both returned progressively to normal regardless of whether ACTH was administered or not. The failure of ACTH to depress total or esterified cholesterol or to retard their return to normal is in contrast to the results of Conn et al. in patients without liver disease¹⁶ in whom short-term ACTH administration produced a sharp decrease below normal, especially of the ester fraction. They are, however, in accord with the findings of Adlersberg et al.¹⁷ in patients receiving more prolonged ACTH therapy.

Globulin: The values for "gamma globulin" measured as units of zinc sulfate turbidity and for globulin measured in serum protein determinations both showed a definite decrease under ACTH therapy as compared with values of control cases. This is shown in figure 3e and f.

RELAPSE

The term "relapse" will be used here to designate the recurrence or recrudescence after an initial period of improvement of clinical signs and symptoms of hepatitis, confirmed by definite changes in liver function tests. By this criterion no patient in the prior group of 200 controls had a relapse, and none occurred in the 20 alternate controls, although one patient returned from the Reconditioning Center with right upper quadrant distress and some hepatomegaly unassociated with changes in liver function tests. It should not be construed from this that relapses are a unique experience in this hospital. However, during the present regimen, with its prolonged period of bed-rest and gradual increase of physical exercise, they have been uncommon. In a previous analysis of over 3,000 patients with hepatitis studied at this Center,¹⁸ a moderately severe relapse was noted in under 1 per cent. In contrast to the control groups, four relapses occurred in the

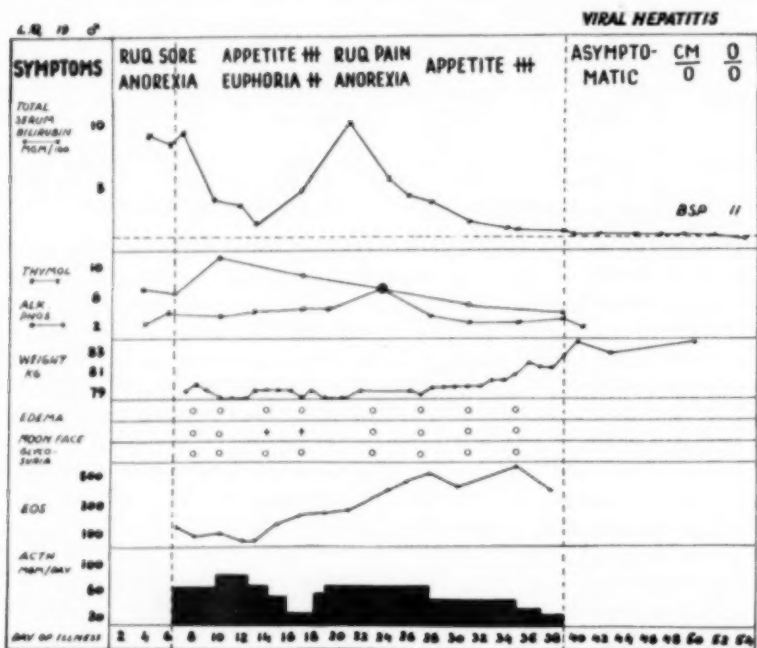
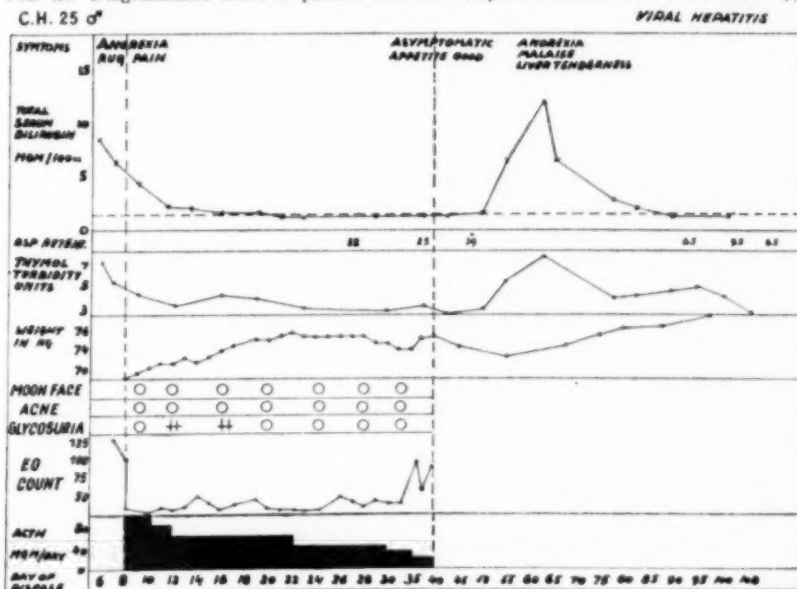
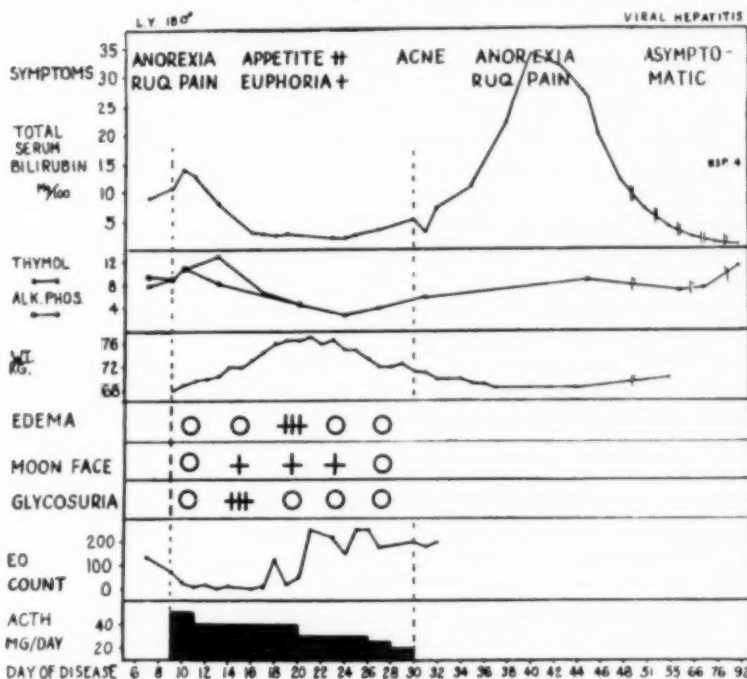


FIG. 4a. Diagrammatic chart of patient who had relapse associated with ACTH therapy.



20 patients treated with ACTH, three with jaundice and the fourth with clinical symptoms, enlargement of the liver and an increase in bromsulfalein retention from 10 to 25 per cent. All four cases were in Group I, in which ACTH was started 10 days or less after onset of symptoms. The courses of the three patients with recurrent jaundice are diagrammatically represented in figure 4a, b and c. One relapse was retreated with ACTH and responded satisfactorily; the others were untreated and made uneventful recoveries. It should be noted that all three relapses with jaundice were more severe than the original illness as measured by serum bilirubin. In patient 6 (see figure 4b), recurrent bilirubinemia reached a peak of 34.2 mg. per cent, as compared with an initial high of 14.6 mg. per cent.

The time of occurrence of relapses was variable: one relapse occurred during lowering of dosage, one at the end of 21 days' treatment, and one about 10 days after a 28 day period of treatment. The anicteric relapse occurred 42 days after a 28 day period of ACTH administration. Two of these four patients had shown a satisfactory eosinophil response, and two had not. The only apparent common denominator favoring a relapse was the fact that they were all started on ACTH within 10 days of the onset of symptoms. Later experience has shown, however, that relapses may also occur when patients are started on such therapy much later in the disease.

EFFECT OF ACTH ON THE HISTOPATHOLOGY OF THE LIVER

As already mentioned, two liver biopsies were performed on each of the 20 patients of Group I. The second biopsy was obtained approximately 30 days after the first, at the completion of ACTH therapy or of control injections, and an average of 39 days after the onset of symptoms. The variation of morphologic findings between cases was more marked in the second biopsy than in the first.

For the sake of brevity, the complete grading on each second biopsy specimen is not presented here; instead, the average group score for each pathologic feature was calculated and the resulting score for the two groups of patients is listed in table 4. Our system of grading is such that a higher numerical score corresponds to a greater intensity of the pathologic process. The table indicates that ACTH in the régime employed in this study did not enhance the repair of the morphologic alterations of the liver. Even if the cases which relapsed are excluded, control and ACTH treated patients show about equal progress towards healing. The only histologic changes which were apparently influenced by ACTH were those connected with fat deposition in the liver cells, which was twice as severe in the ACTH group as in the control group.

A satisfactory progress toward healing was evident in the second biopsy specimen of all 10 patients of the control group, and in eight of the 10 patients on ACTH therapy. One of the exceptions was that of patient 6 (figure 4b), who had a severe relapse coincident with the discontinuance

of ACTH therapy, and whose second biopsy was obtained at the height of the recurrent bilirubinemia. This section showed evidence of an acute early hepatitis plus a marked widening and fibrosis of the periportal fields, combined with a high degree of bile duct proliferation. Such features are not seen in an early acute phase of uncomplicated hepatitis, and have to be attributed in part to the preceding attack. A second treated case, patient 7, in whom no relapse had occurred, also showed morphologic findings which were at variance with the remainder of the cases. Here, as in the preceding patient, the principal difference was the marked widening of the periportal fields and a rather striking degree of bile duct proliferation at the expense of lobular parenchyma. The resulting picture resembled findings which have been described by Watson and Hoffbauer¹⁹ as cholangiolitic hepatitis. In contrast to the prolonged course in their cases, this patient had a delayed but otherwise uneventful recovery. In addition, this patient, unlike all other cases of Group I receiving ACTH, showed no drop in serum bilirubin

TABLE IV
Average Group Scores in Histologic Grading of Posttreatment Liver Biopsies
Obtained from 10 ACTH Treated and from 10 Control Patients

	ACTH	Control
Disorganization of architecture	2.3	1.8
Focal liver cell necrosis	2.0	1.6
Intralobular inflammatory reaction	2.0	1.5
Focalization	1.4	0.9
Thickening	1.5	1.4
Reactive	2.4	1.7
Fat	1.1	0.5
Periportal fibrosis	2.3	2.1
Periportal inflammatory reaction	1.9	1.6
Bile duct proliferation	1.9	1.5

coincident with therapy and evidenced none of the physiologic side effects such as eosinopenia, glycosuria, etc.

In addition to the case described above, three others experienced a relapse of their disease. The first, patient 1 (figure 4a), relapsed while the dosage of ACTH was being reduced, and the second biopsy was obtained about 23 days after the onset of the recurrence and 18 days after the bilirubinemia had reached its second peak. The morphologic findings at this time were compatible with a normal evolution of the disease. All features noted could be attributed to the effect of an uncomplicated case of viral hepatitis of about three weeks' duration, and it was impossible to tell that a relapse had occurred. The two other cases suffered relapses some time after the discontinuance of ACTH. In one, patient 10 (figure 4c), in whom the liver biopsy was obtained about two weeks preceding the onset of relapse, the changes were still moderately severe; in the other, patient 8, in whom an anicteric relapse occurred 11 days after the second biopsy, the morphologic alterations were severe. In neither of these cases, however, were special

features seen by which the relapse could have been predicted, and the histologic changes were not materially different from cases of similar severity in the treated as well as in the control group who had made an uneventful recovery. In patient 8, whose second biopsy showed the most severe changes, a third biopsy obtained on the one hundredth day of illness, 46 days after the beginning of the relapse, showed that morphologic recovery was well advanced. It was impossible to tell from this slide that the patient had had a relapse.

A special feature shown by three patients of the treated group (cases 1, 3 and 10) was the presence of a moderately severe degree of fatty metamorphosis of the liver cells which had not been present in the pretreatment biopsy. Fatty metamorphosis of similar degree was not observed among the control group. Two of the cases showing this change had suffered a relapse, but in one the biopsy had been obtained prior to this event. The third case showing fatty metamorphosis had not relapsed and had made a

TABLE V
Physiologic Side Effects of ACTH

Effect	Per Cent of Cases Showing Effect		
	Group I (10 cases)	Group II (10 cases)	Average (20 cases)
Glycosuria	80	80	80
Euphoria	90	60	75
Eosinophil response	20	80	50
Rounding of face	50	50	50
Acne	20	80	50
Hyperglycemia	50	30	40
Hypertension	30	30	30
Edema	30	0	15
Aching of joints	0	10	5
Flushing of face	0	10	5

rapid and uneventful recovery. The effect of ACTH on fat metabolism has been summarized by Archer,²⁰ and our findings are in agreement with the work cited in his paper.

PHYSIOLOGIC EFFECTS

The physiologic effects induced by ACTH in patients with viral hepatitis were similar to those reported in other diseases,²¹ except that disturbances in carbohydrate metabolism were more striking and the eosinophil response was much poorer. The over-all physiologic effects are shown in table 5. It was not necessary to discontinue ACTH in any patient because of undesirable side effects, but in several instances the dosage was reduced because of edema or hypertension. The physiologic effects are discussed in more detail below.

Euphoria: Fifteen of the 20 patients receiving ACTH showed a notice-

able improvement in well-being, and this was usually accompanied by an increase in appetite at times almost insatiable. Despite this, weight gain was not better than in the control group, except for three patients who developed edema. It should be pointed out that, contrary to many textbooks, the majority of our patients with hepatitis have a good appetite after an initial period of about a week, and can cope ably indeed with the 4,200 calorie diet given them.

Eosinophil Response: Four of 20 untreated control patients had absolute eosinophil counts below 100 per cubic millimeter at some time during the three to four week period of testing. The lowest counts recorded for these four patients were 38.5, 44, 49.5 and 49.5. These low counts were very transient in character and were usually seen only early in the disease. Thus, viral hepatitis was not accompanied by a marked eosinopenia, as is the case with some other infectious diseases.²²⁻²⁴

The eosinophil response to ACTH was, in general, poor. Only seven of 20 patients showed a prolonged drop in eosinophils of over 50 per cent. In these, this low count persisted for from 17 to 25 days. One other patient had a similar drop lasting eight days on ACTH. The other 12 patients showed a negligible or transient effect or no effect at all. The capacity of ACTH to induce eosinopenia did not appear to be correlated with the clinical result obtained as measured especially by decrease in serum bilirubin values.

Carbohydrate Metabolism: In the control group of 20 patients, one showed persistent glycosuria during the early phase of the disease, and transient glycosuria was seen in four others. No patient had hyperglycemia. In contrast, 16 of the 20 patients treated with ACTH had well marked glycosuria; seven of these had fasting hyperglycemia and six others had elevations in the two hour postcibal sample. Glycosuria frequently disappeared while the patient was still under ACTH therapy. No patient was left with disturbances of carbohydrate metabolism at the time of discharge.

The high incidence of such disturbances in hepatitis patients treated with ACTH is in contrast to the reported effects of this drug in nonhepatic diseases. For example, Rosenberg et al.²¹ noted glycosuria without hyperglycemia in only 7.1 per cent of 211 patients given ACTH. The frequency in our series is probably related to disturbances in carbohydrate metabolism, especially glycogen storage, incident to viral hepatitis, and in part perhaps to the very high carbohydrate diet given. Similar disturbances in sugar tolerance have been reported with ACTH therapy in chronic liver disease by Bongiovanni and Eisenmenger,³ and all five of the acute hepatitis cases treated by Colbert et al.⁷ with this drug had glycosuria.

Hypertension: Elevations of basal blood pressure to 140/90 mm. of Hg or more occurred in six patients treated with ACTH (30 per cent). In one case the increase was quite striking, rising from a baseline of 110/64 to 154/88 mm. of Hg by the sixth day of treatment. Despite a daily dose of ACTH of only 30 mg., the blood pressure continued to rise, reaching a

peak of 190/122 mm. of Hg on the twenty-fourth day of treatment, and this was accompanied by nervousness, insomnia, palpitation and headache. Levels of 140/90 mm. of Hg persisted for a week after discontinuance of ACTH. There was no familial history of hypertension.

Edema: Three patients, all in Group I, showed demonstrable edema while on ACTH. In the first it appeared suddenly and was of marked degree in ankles, scrotum and penis, interfering with urination and associated with a weight gain of 23 pounds. Daily ACTH dosage was lowered from 40 to 20 mg., with disappearance of edema and a weight loss of 21 pounds in five days. In the second patient a weight gain of 18 pounds was associated with 2 plus edema of the ankles. Lowering of dosage from 60 mg. to 40 mg. resulted in a weight loss of 11 pounds in seven days. Further reduction effected a further loss of 6.6 pounds in the next week. In the third patient a weight gain of 12 pounds occurred, with only transient ankle edema.

Other physiologic effects, such as acne, rounding of the face, etc., are listed in table 5 and require no further comment here.

One patient, who had shown no physiologic effects from ACTH except for transient eosinopenia and questionable euphoria, and no apparent changes in clinical or laboratory status attributable to this therapy, had a striking reaction the day after its discontinuance. This consisted of severe frontal and retroorbital headache, malaise, fever of 102° F. and slight pain in the chest on breathing. Questioning revealed an episode of polyarthritides and fever one month prior to the hepatitis. Physical examination was completely normal except for hepatomegaly. These symptoms persisted for five days, then disappeared without therapy. All studies during this period were negative, including complete blood counts, urinalysis, blood and sputum cultures, agglutination tests for enteric organisms before and after illness, chest x-rays, electrocardiograms and examination of spinal fluid. A liver biopsy performed a week after onset of these symptoms revealed a subsiding hepatitis, with very slight inflammatory reaction. About one month after discontinuance of ACTH this patient developed right lower quadrant pain and tenderness. The appendix was removed uneventfully and revealed an acute phlegmonous appendicitis. The subsequent course of the patient was uneventful except for persistent hepatomegaly of about one fingerbreadth.

DISCUSSION

In this paper it has been shown that 18 of 20 patients with acute viral hepatitis treated with ACTH had a prompt and often dramatic initial drop in serum bilirubin as compared to control groups. This was accompanied by symptomatic improvement. The total duration of illness in ACTH-treated patients as a whole was not shorter than in patients not receiving this compound.

Analysis of the course of illness in the 10 patients started on ACTH in the first 10 days of illness (Group I) revealed differences from the 10 patients

started on therapy in the second 10 days of illness. When ACTH was begun in the earlier period there was a tendency toward prolongation of disease, side effects were common, and four relapses occurred. When therapy was started later, the duration of bilirubinemia was significantly shorter than in control patients, side effects less severe and, with one exception, the bromsulfalein test returned to a value of 10 per cent or less two weeks earlier than in the control groups. No relapses were encountered in this group, although later experience has shown that delaying the initiation of hormone therapy does not necessarily prevent their occurrence.

Pathologic studies carried out at the beginning and end of ACTH or of control injections in Group I failed to reveal significant differences between treated and control groups, with the exception that fatty metamorphosis was observed in the second biopsy of three of the patients receiving ACTH. Since no similar changes occurred in the control group, this phenomenon is presumably related to the administration of ACTH. No prediction of the final outcome of the disease could be made on the basis of biopsies taken early in the disease, and even in two second biopsies, taken 10 to 14 days before the occurrence of a relapse, no special features were seen that foreshadowed this event.

The limitation of the predominant effect of ACTH to the first weeks of administration, as evidenced by the serum bilirubin response and the increase in eosinophil counts above pretreatment level as therapy was continued, suggests the possibility that the adrenal gland might respond progressively less well to prolonged ACTH therapy in patients with hepatitis. If this concept had any validity, direct substitution therapy, as with cortisone might be expected to yield better results. This problem is investigated in the next paper of this series.

SUMMARY

1. Twenty patients with acute viral hepatitis were treated with ACTH in strict alternation with 20 similar control patients who received injections of saline. Half of the patients were started on injections in the first 10 days after onset of illness, half in the second 10 days. The results in these groups were further compared with a control group of 200 similar cases admitted prior to the study. One hundred of these were admitted in the first 10 days of illness, 100 in the second 10 days of illness.

2. ACTH therapy was associated with a prompt drop in serum bilirubin in 18 of the treated patients, as compared to control groups. The time taken for apparent clinical recovery, complete disappearance of jaundice and return of bromsulfalein retention to 10 per cent or less was somewhat longer in patients started on ACTH early in disease than in the control groups, and was about 10 days shorter than the controls in patients started on ACTH later in the disease.

3. Four clinical relapses, three with jaundice, occurred in 10 cases in

which ACTH therapy was started in the first 10 days of illness. No clinical relapse occurred in 10 patients treated with ACTH later in the disease, and none in the combined group of 220 control patients.

4. Liver biopsy studies done in the 10 early cases at the beginning and end of ACTH therapy did not differ appreciably from 10 control patients similarly studied, except insofar as fat deposits in the cells were concerned.

5. The physiologic effect of ACTH in the 20 treated cases was notable in two respects: (a) only seven patients showed a good eosinophil response; (b) glycosuria occurred in 16 patients and fasting hyperglycemia in seven patients.

ADDENDUM

A preliminary report of the first 10 cases has been made at the Second Middle East Medical Symposium, American University of Beirut, Lebanon, November 9-11, 1951. (See Evans, A. S.: Viral hepatitis. General aspects and the effects of ACTH on the course of the disease, *Lebanese M. J.* 5: 53, 1952.)

ACKNOWLEDGMENT

Acknowledgment is made to Maj. General Guy B. Denit, Chief Surgeon, USAREUR, for his continuous interest and encouragement in this work; to Colonel Emery E. Alling, Colonel William S. George and Colonel James D. Gardner, of the 98th General Hospital, for their active support, and to the following physicians of the Hepatitis Section for their assistance: Lieutenant Morton N. Swartz, Captain John W. Callister, Dr. Guenter Blume and Dr. Karl-Heinz Ronde. We also wish to thank Mrs. Mara Iwan for clerical help.

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ADRENAL HORMONE THERAPY IN VIRAL HEPATITIS. II. THE EFFECT OF CORTISONE IN THE ACUTE DISEASE*

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In the preceding paper¹ it has been shown that administration of adreno-corticotrophic hormone (ACTH) to 20 patients with acute viral hepatitis was associated with symptomatic improvement and a rapid initial drop in serum bilirubin as compared with control patients. This effect on bilirubinemia became progressively less marked as the drug was continued. The eosinophil response was, in general, poor. The average total duration of illness was not materially affected. It seemed possible that adrenal cortical exhaustion was responsible in part for these phenomena, and that direct substitution therapy with cortisone might be more effective and at the same time lessen the disturbances of mineral metabolism encountered with ACTH. For these reasons a controlled clinical pathologic study of the effect of cortisone in 10 patients with early acute viral hepatitis has been carried out, the results of which will be presented in this paper.

MATERIALS AND METHODS

The general plan of investigation, including clinical, laboratory and pathologic studies, and the selection and management of control cases, was similar to that of the preceding study.¹

Criteria of Patients Studied: All patients, both the cortisone-treated and the control groups discussed below, met the following criteria: (1) characteristic viral hepatitis as evidenced by history, physical examination, and appropriate changes in liver function tests, and as confirmed by liver biopsy in the case of cortisone-treated and alternate controls; (2) a total serum bilirubin of 5 mg. per cent or more at the start of hormone injections or of the control period, every effort being made to select only cases with a demonstrably rising serum bilirubin; (3) a duration of illness of not more than 10 days at the time that injections or control period was started.

Control Groups: There were three control groups: (1) Seven patients admitted in strict alternation with the first seven cortisone-treated patients who received control injections of cholesterol suspension.‡ (2) Ten other similar patients who had been admitted and treated in alternation with patients receiving ACTH immediately prior to the cortisone study. They

* Received for publication December 2, 1952.

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‡ Cholesterol suspension was kindly furnished by Merck and Co., Rahway, New Jersey.

were given control injections of saline. These 17 control patients will be referred to as the alternate control group in order to carry over the terminology used in the preceding paper. (3) One hundred similar patients with serum bilirubin values over 5 mg. per cent in the first 10 days of illness who had been admitted just prior to the ACTH-cortisone investigation. This group, called the "prior control group," differed from the study group in the following respects: (1) a diet unlimited in salt was allowed; (2) control solutions were not given; (3) liver biopsies were not performed, and (4) laboratory studies were carried out less frequently. In this group it was also not possible to select only patients with a rising serum bilirubin.

The diet for cortisone-treated and alternate control patients was the same and has been previously described.¹ Cortisone and control solutions were given over a continuous period of at least 28 days, except in a few control

TABLE I
Pretreatment Data for Cortisone and Control Patients

	Cortisone Treated	Control	
		Alternate	Prior
Number of patients	10	17	100
Age	23.9	22.6	23.9
Day of disease*	8.10	8.35	7.70
Total serum bilirubin (mg. %)	9.41	8.02	8.40
1' Serum bilirubin (mg. %)	5.11	4.57	4.50
Thymol turbidity (units)	12.04	10.60	10.90
Cephalin flocculation (24 hrs.)	2.25	2.34	2.30
Alkaline phosphatase (units)	7.53	8.65	8.70
"Gamma globulin" (units)	12.89	13.50	—
Cholesterol esters (%)	42.30	41.80	—

— Indicates sufficient data not available.

* Day of disease indicates the average day after onset of illness on which the cortisone group of patients and the alternate control group of patients were given their first injection and the day on which initial laboratory studies were done in the prior control group.

patients in whom control injections were given for only 21 days. In nine of the 10 patients receiving cortisone the dosage plan was as follows: 100 mg. was given every eight hours the first day, every 12 hours the second day, and then once daily through the twenty-fifth day. On the twenty-sixth day the dose was reduced to 75 mg., on the twenty-seventh day to 50 mg., and on the twenty-eighth day to 25 mg. Small doses of ACTH were given, in addition, to one patient on the last two days of cortisone administration. The tenth patient received a similar schedule of treatment to the twenty-third day, then 75 mg. twice daily through the thirty-eighth day, then a dosage decreasing 25 mg. every other day to completion of therapy on the forty-ninth day. During the period of decreasing dosage this patient also received daily infusions of 1,000 ml. of 10 per cent glucose in distilled water.

Liver biopsies were done at the beginning and end of cortisone administration in nine of the 10 treated patients. In two cases the second

biopsy was unsuccessful or inadequate. Liver biopsies were done successfully at similar time intervals in 16 of the 17 alternate control patients. No complications of the procedure were encountered, and no delay in healing of the biopsy wound was seen in patients receiving cortisone.

PRETREATMENT STATUS

Certain features of the cortisone group of patients and the alternate control group at the start of the treatment period are shown in table 1, as well as similar data obtained on admission in the 100 prior control cases. At that time there was a close similarity between patients who later received cortisone and those serving as controls, with the exception that the intensity of the jaundice was slightly greater in the cortisone group, as shown by a serum bilirubin of about 1.0 mg. per cent higher than the controls; the range of this test for both treated and alternate control cases was from 5 to 15 mg. per

TABLE II
Results of Cortisone Therapy in Acute Viral Hepatitis as Compared with Control Groups

Group	Number of Cases	Day of Disease When Test Returned to Normal and Presence of Statistical Difference (SD) of Cortisone from Control Groups*				Day of Disease When Ready for Discharge	Relapses in Group†
		Total Serum Bilirubin (1.00 mg. or less)		BSP Retention (10% or less)			
		Day	S.D.	Day	S.D.		
Cortisone	10	31.7		42.3		52.7	2
Alternate control	17	45.7	Yes	56.8	No	69.7	0
Prior control	100	45.3	Yes	53.7	No	N.C.	0

BSP = Bromsulfalein. N.C. = Not calculated.

* Presence of statistical difference indicates whether the cortisone-treated group differed significantly from either control group. This was computed by a T test to indicate statistical significance at the 5% level.

† This includes late relapses.

cent, three of the alternate control group and two of the cortisone-treated group having values over 10 mg. per cent.

RESULTS OF TREATMENT

The effect of cortisone therapy on the course of acute viral hepatitis is compared in table 2 with the course of illness in patients not receiving this compound. The data indicate that the average duration of jaundice, measured as the time taken to return to a normal total serum bilirubin, was two weeks shorter in cortisone-treated patients than in the alternate control group, and also two weeks shorter than in the prior control group; in each instance this difference was statistically significant.* Similarly, patients

* Statistical analyses were made independently by Major William A. Haendiges, 98th General Hospital, and by the Statistical Section, Armed Forces Institute of Pathology, through the courtesy of Lt. Colonel C. F. Vorder Bruegge.

receiving cortisone reached a bromsulfalein retention of 10 per cent or less about two weeks sooner than control groups. In this instance the differences were not significant, because one treated patient had prolonged bromsulfalein retention for 93 days; the range of the other nine cases was 25 to 57 days. Thus, cortisone therapy was associated with a definitely accelerated disappearance of jaundice in all 10 patients, and with an accelerated return of bromsulfalein excretion toward normal in nine of the 10 patients, as compared with the natural course of illness in control groups. Improvement to the point where our criteria † for discharge to a Reconditioning Center were fulfilled occurred 17 days earlier in the patients receiving cortisone than in patients receiving control injections of saline or cholesterol. Similar data were not available for the prior control group nor was a statistical analysis made.

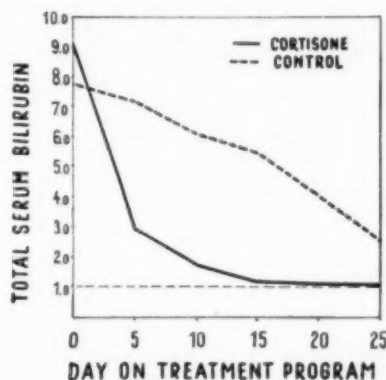


FIG. 1. Effect of cortisone on total serum bilirubin in 10 patients as compared to 17 control patients.

The fact that patients treated with cortisone met certain criteria of improvement about two weeks sooner than those not receiving this compound should be viewed in the light of one very important consideration, namely, the occurrence of *two relapses* in the 10 patients who received this drug, as compared to *no relapses* in the combined control group of 117 patients. One of these relapses occurred while the patient was under cortisone administration and is included in the analysis presented above; the second occurred one month after discontinuance of cortisone, while the patient was in a Reconditioning Center, and only the initial recovery time in this patient was used in the results of table 2. If the total length of illness of this patient is considered in the calculations, the difference in recovery times between the cortisone-treated group and the control groups would be approximately a week.

† Criteria for discharge to a Reconditioning Center include a normal serum bilirubin, two consecutive bromsulfalein tests under 10 per cent, a nontender liver not more than one fingerbreadth enlarged, and an asymptomatic status.

A more detailed description of certain of the effects of cortisone therapy is given in the next section.

EFFECT OF CORTISONE ON LIVER FUNCTION

Serum Bilirubin: All 10 patients treated with cortisone had a prompt and often dramatic fall in total serum bilirubin (TSB), most marked during the first 10 days of therapy and then continuing slowly until a normal value was reached, except for one case that relapsed on the fifteenth day of treatment. The average total serum bilirubin dropped from 9.17 mg. per cent on the day therapy was started to 2.80 mg. per cent on the fifth completed day of therapy, as shown in figure 1.

In contrast, there was great variation in the return of serum bilirubin to normal in the control group: some showed an initial rise, others a slow fall, and a few a rapid fall. The latter cases emphasize the need for adequate controls in such a study. The magnitude of the effect of cortisone on serum

TABLE III
Decrease in Percentage of Total Serum Bilirubin at Five Day Intervals
as Estimated from Initial Values

Day on Program	Per Cent Decrease in Serum Bilirubin		
	Cortisone (10)	Alternate (17)	Prior (100)
0	0	0	0
5	67.5	7.6	16.4
10	81.9	19.5	35.6
15	86.7	37.0	55.9
20	86.9	49.2	67.8
25	86.7	67.0	78.6

(10) (17) (100)—Refer to number of patients in group.

bilirubin is perhaps best emphasized by calculating the decrease in percentage of total serum bilirubin, taking the pretreatment value as the base line. The total serum bilirubin on the day of admission was taken as the base line for the 100 prior controls. These data are presented in table 3. As shown, the serum bilirubin dropped an average of 67.5 per cent by the fifth day of treatment in patients receiving cortisone, while a similar decrease was not seen in either control group until at least three weeks later. The consistency of the response is demonstrated by the fact that the serum bilirubin in all 10 cortisone-treated patients had decreased to at least 50 per cent of the starting level by the fifth day of administration, while only three of the 17 alternate control patients had shown a similar decrease at this point.

Bromsulfalein Excretion: The average patient treated with cortisone reached a level of 10 per cent dye retention or less two weeks sooner than either control group. This result was in contrast to that with ACTH, in which the effect on dye excretion appeared to lag behind the effect on serum

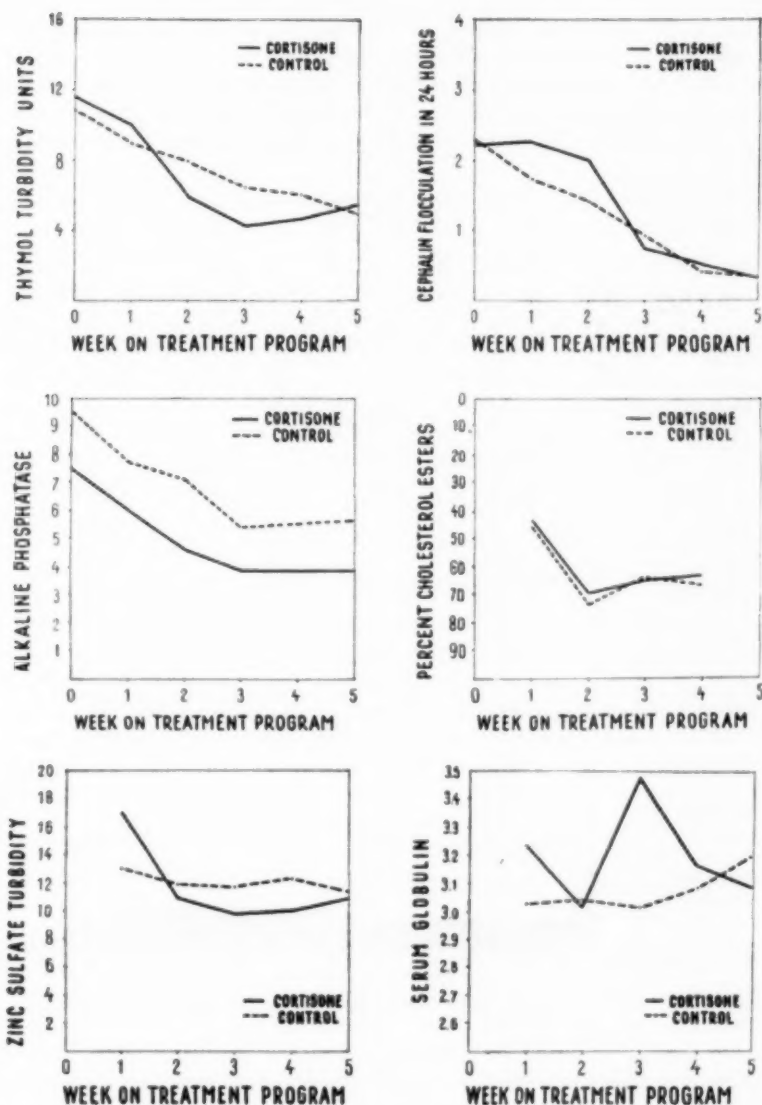


FIG. 2. Course of certain liver function tests in 10 patients given cortisone over a four week period as compared with 17 similar control patients.

bilirubin. In two patients given cortisone the bromsulfalein test was performed weekly from the start of therapy and the results were corrected for the presence of jaundice. It was found that the decrease in the corrected bromsulfalein retention roughly paralleled the rapid fall in serum bilirubin.

Effect of Cortisone on Other Liver Function Tests: The results of cortisone administration on thymol turbidity, cephalin cholesterol flocculation,

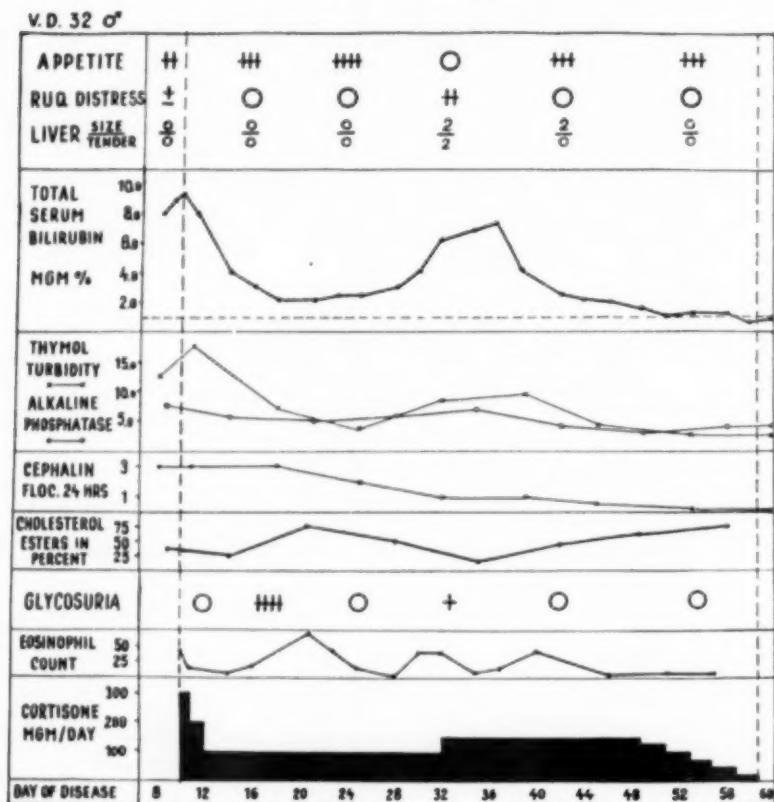


FIG. 3. Effect of cortisone on the course of viral hepatitis in patient 10.

alkaline phosphatase, per cent cholesterol esters, "gamma globulin" (measured as zinc sulfate turbidity) and serum globulin, as compared to the alternate group, are shown in figure 2. Because of limitations of time and laboratory facilities, some of these tests were not performed until a few days after the treatment program was begun; thus the results fell into the first week of treatment, rather than representing true pretreatment values. In these instances no base line determination is shown. As indicated in the

figures, no significant differences in these tests in cortisone-treated and control patients were observed, with the possible exception of both the "gamma globulin" and the serum globulin, in which cortisone appeared to produce an initial drop. A similar effect was observed in patients treated with ACTH, in whom the effect was more sustained.¹ The secondary rise in the serum globulin fraction in patients treated with cortisone is unexplained and did not occur with ACTH.

RELAPSES

As mentioned earlier in this paper two relapses occurred in the group of 10 cortisone-treated patients, with recurrence of clinical symptoms, increasing jaundice, and appropriate changes in liver function tests. No such relapses occurred in the combined control groups of 117 patients. The first relapse was in a patient who had shown an excellent initial response to cortisone and who had been discharged to a Reconditioning Center as presumably having recovered from viral hepatitis. While there, and about one month after cortisone had been discontinued, he developed malaise, bromsulfalein retention increased, and finally jaundice reappeared. On re-admission to the hospital, recurrent bilirubinemia reached 3.96 mg. per cent. He recovered uneventfully from his relapse without cortisone therapy. The second relapse occurred in a patient who had been receiving a constant daily dose of 100 mg. of cortisone for about two weeks preceding this event. His case is graphically presented in figure 3. It will be noted that the serum bilirubin decreased rapidly from 9.5 mg. per cent to 2.23 mg. per cent in the first week of treatment, then remained unchanged for about a week, then rose again to a high of 7.26 mg. per cent at which time the patient had malaise, anorexia, right upper quadrant distress and an enlarged and tender liver. Increase of cortisone to 150 mg. daily resulted in symptomatic relief without euphoria, and a second drop in serum bilirubin occurred. After about two weeks at this increased level, cortisone dosage was gradually reduced in conjunction with daily glucose infusions, and was finally discontinued after 49 days of administration. The subsequent course of this patient was uneventful.

EFFECT OF CORTISONE ON HISTOPATHOLOGY OF THE LIVER

The pretreatment liver biopsies obtained from patients to be given cortisone presented findings similar to those obtained from patients serving as controls. Such changes have been described in our preceding paper. All cases presented evidence of an early phase of acute viral hepatitis. Some variation existed between individual specimens, but as a whole the two groups were closely comparable. A greater degree of variation between the two groups was noted in the post-treatment biopsy.

The histologic grading system employed was designed to indicate the severity of certain features believed to be associated with activity of the

disease process. A high score thus indicated continued evidence of inflammation, a low score progress toward healing. For the sake of brevity, the complete data on each individual case are not presented, but only the average group score for the various pathologic features of the seven cortisone-treated patients, including one relapse, and the 17 control patients. Similar data were determined for the ACTH group reported in the preceding paper. The results are listed in table 4. Cortisone-treated patients showed the greatest progress toward recovery, despite the occurrence of one relapse in this group. Comparison of the individual cases in this group revealed fairly uniform histopathologic findings excepting the relapse. The degree of variation between individual cases, as well as the variation from normal, was less in the cortisone-treated group than in either the ACTH treated group or the alternate control group. The histologic findings confirm the impression gained by the clinical and laboratory investigations that cortisone therapy

TABLE IV
Average Group Scores in Histologic Grading of Posttreatment Liver Biopsies Obtained from ACTH and Cortisone Treated Patients and from Control Patients

	Control (17)	ACTH (10)	Cortisone (7)
Disorganization of architecture	1.75	2.3	1.14
Focal liver cell necrosis	1.50	2.0	1.00
Intralobular inflammatory reaction	1.50	2.0	1.14
Focalization of intralobular inflammatory reaction	1.06	1.4	1.43
Thickening of intralobular connective tissue fibrils	1.31	1.5	1.14
Reactive liver cell pleomorphism	1.62	2.4	1.57
Periportal fibrosis and widening	2.19	2.3	1.86
Periportal inflammatory reaction	1.56	1.9	1.28
Bile duct proliferation	1.69	1.9	1.00

was associated with a more rapid progress toward apparent recovery than in the control group. A special feature of the cortisone group was the presence of fat vacuolation in liver cells, which was twice as marked as in the ACTH group and four times as marked as in the alternate control group. The group score for this feature was 2.0 for cortisone, 1.1 for ACTH, and 0.44 for the control patients. The origin of the fat and its significance with regard to the healing of hepatitis are unknown. As mentioned in our preceding paper, these hormones have an effect on lipid metabolism probably by influencing fat mobilization from peripheral depots.

PHYSIOLOGIC EFFECTS

The physiologic response to cortisone in 10 patients with acute viral hepatitis is compared in table 5 with the responses of 10 patients treated with ACTH in a similar phase of the disease,¹ as well as with 17 similar patients receiving control injections of saline or cholesterol. Only a few

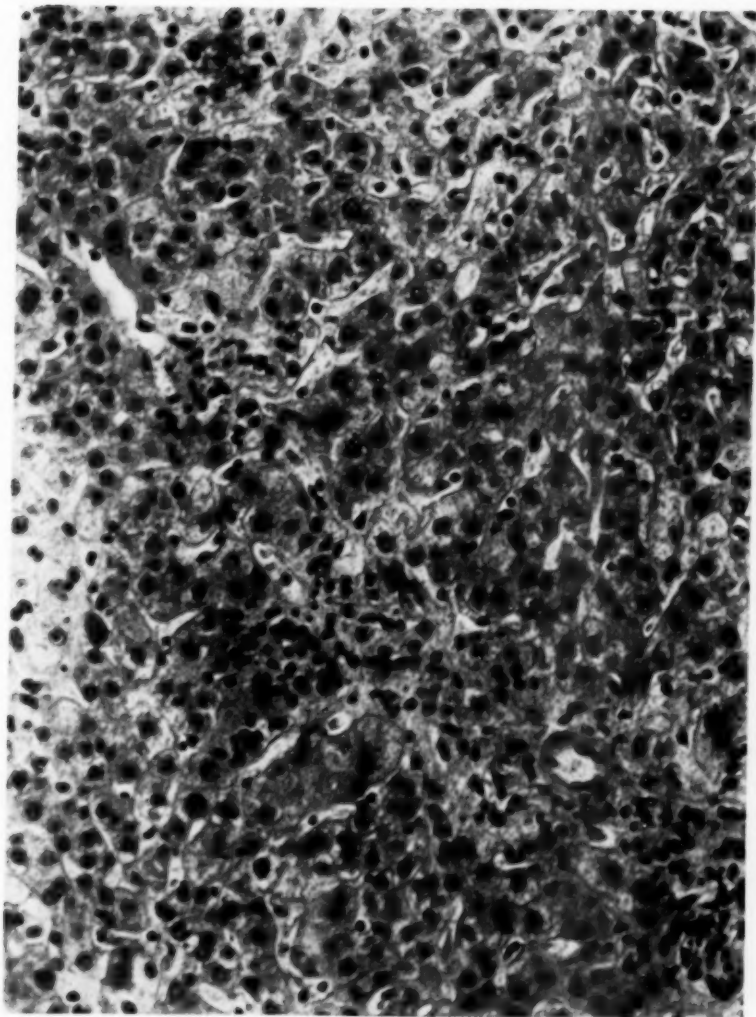


FIG. 4a. Liver biopsy of patient 2 prior to cortisone therapy, eighth day of illness.

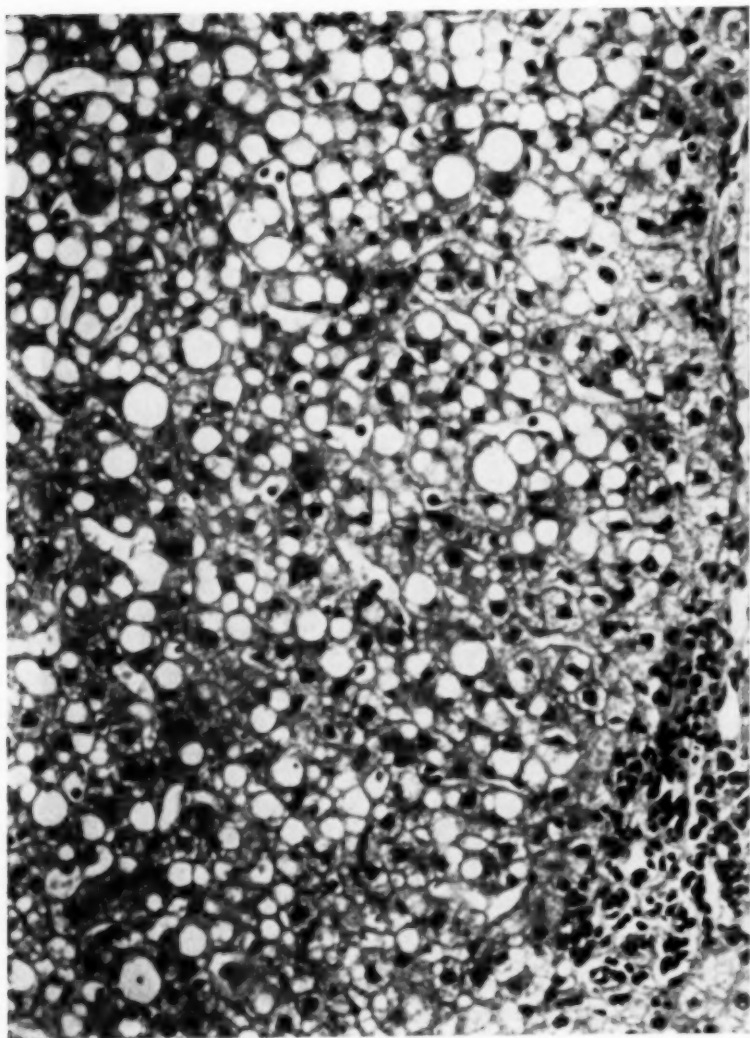


FIG. 4b. After 28 days of cortisone therapy (thirty-seventh day of illness). Note fat vacuolation.

features of the side effects of cortisone will be considered here, since they were in general similar to those of ACTH discussed in more detail in the preceding paper.

The inherent tendency of patients in early viral hepatitis to disturbances in carbohydrate metabolism was markedly exaggerated by cortisone administration. All 10 treated patients had glycosuria, three had fasting hyperglycemia, and two additional patients had hyperglycemia two hours after breakfast. These disturbances in sugar tolerance usually disappeared despite continuous administration of the same dosage of cortisone.

The eosinophil count fell to levels of 50 per cent or less of the pretreatment values in six of 10 patients receiving cortisone during the first week of administration. After a week of therapy only one patient had persistent eosinopenia. In the control group, six of the 17 patients had transient

TABLE V
Physiologic Effects of Cortisone Therapy as Compared to ACTH Therapy
and to a Control Group

Type of Effect	Per Cent of Cases Showing Effect		
	Cortisone (10 cases)	ACTH* (10 cases)	Control (17 cases)
Glycosuria	100	80	23
Euphoria	70	90	10
Rounding of face	70	50	0
Eosinopenia	60	20	0
Acne	40	20	0
Hyperglycemia	30	50	6
Hypertension (over 140/90)	20	30	0
EKG changes	20	20	0
Edema	0	30	0

* These 10 cases were treated in a phase of disease similar to that of the cortisone cases. Ten other cases, treated later in the disease with ACTH, are not included in this table.

lowering of the eosinophil counts below 100, but these could not be related to the control injections.

Frank edema or rapid weight gain was not encountered in patients receiving cortisone. In contrast, three of 10 patients who had received ACTH in a similar phase of disease had shown edema, and in two it had been severe enough to necessitate lowering the dosage.¹

Other side effects of cortisone therapy are listed in table 5, and require no further comment. In no instance were the untoward physiologic responses to cortisone considered serious enough to alter the dosage schedule.

DISCUSSION

The administration of cortisone to 10 patients with early acute viral hepatitis was associated with the disappearance of bilirubinemia, the return of bromsulfalein retention to 10 per cent or less, and the fulfillment of criteria

used in this hospital as a basis for discharge to the Reconditioning Center some two weeks sooner than a group of 17 simultaneously studied patients receiving control injections, or a group of 100 similar patients admitted prior to this study. Pathologic studies at the beginning and end of cortisone administration and at a similar time in the alternate group were in agreement with the clinical and laboratory studies: a distinct and uniform tendency towards early healing was seen in all specimens from cortisone-treated patients, with the exception of one biopsy taken at the time of relapse. In contrast, liver biopsies from control patients as well as from patients treated with ACTH showed a greater variability in morphologic findings without a consistent tendency toward uniform healing. Another feature of cortisone treatment was a moderately severe degree of fat vacuolation of liver cells, twice as great as seen under ACTH therapy and four times as great as in the control group.

The question was raised at the beginning of this paper as to whether cortisone therapy might produce better results than had been obtained with ACTH therapy.¹ The data presented indicate that the 10 patients treated with cortisone showed more rapid and more consistent clinical improvement, a more definite tendency toward healing in liver biopsy sections, and less troublesome side effects than the 10 patients started on ACTH in a similar phase of illness (first 10 days after onset of symptoms). However, nine of 10 patients started on ACTH from the eleventh to the twentieth day after onset showed almost as rapid improvement as the cortisone-treated patients described in this paper, and there were no relapses. Liver biopsies were not done in this group. We have no comparable data on patients started on cortisone in this period of disease.

A most serious disadvantage to cortisone therapy was the occurrence of two relapses in the 10 patients treated. No such relapses occurred in the combined group of 117 controls. The frequency and severity of such relapses with both ACTH and cortisone made a profound impression on both patient and physician. The possibility must also be considered that the more rapid return to normal of certain clinical and laboratory features of viral hepatitis under ACTH or cortisone therapy may actually be premature in terms of immunity and resistance. The mechanism by which these hormones might alter host-virus relationships and in such fashion enhance the possibility of relapse could be: (1) actual enhancement of the growth of the virus, (2) interference with immune reactions, (3) a combination of these. Experimental evidence in support of these concepts in other diseases has recently been reviewed.²

SUMMARY

1. The administration of cortisone to 10 patients with early acute viral hepatitis was associated with a prompt fall in serum bilirubin and a primary

recovery period about two weeks shorter than 17 similar patients receiving control injections, or 100 similar patients admitted prior to this study.

2. Histopathologic studies revealed a more rapid progress toward healing in cortisone-treated than in control patients. This was accompanied by a moderately severe degree of fatty metamorphosis.

3. Two relapses occurred in the 10 patients treated with cortisone, none in the combined group of 117 control patients.

4. The theory is presented that while cortisone therapy speeded up the return of certain clinical, laboratory and pathologic features toward normal, it left the patient more vulnerable to relapse than patients not so treated because of disturbances in virus-host relationships important in immunity.

ACKNOWLEDGMENT

Acknowledgment is made to Maj. General Guy B. Denit, Chief Surgeon, USAREUR, for his continuous interest and encouragement in this work; to Colonel Emery E. Alling, Colonel William S. George and Colonel James D. Gardner, of the 98th General Hospital, for their active support; and to the following physicians of the Hepatitis Section for their assistance: Lieutenant Morton N. Swartz, Captain John W. Callister, Dr. Guenter Blume and Dr. Karl-Heinz Ronde. We also wish to thank Mrs. Mara Iwan for clerical help.

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ADRENAL HORMONE THERAPY IN VIRAL HEPATITIS. III. THE EFFECT OF ACTH AND CORTISONE IN SEVERE AND FULMINANT CASES *

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THE present study is concerned with the results of ACTH and cortisone therapy in 11 severe cases of viral hepatitis that had not responded to conservative measures, six of whom ultimately died. The six fatal cases represent the mortality from some 1,500 cases of hepatitis admitted during the period of this investigation. Our decision to treat such patients with adrenal hormone therapy was influenced in part by our results in early acute viral hepatitis,¹⁻⁴ ‡ and in part by a discouraging previous experience with this type of case using only supportive measures.⁵ Reports from other clinics of the beneficial, often dramatic results of adrenal therapy in patients with severe and fulminant hepatitis have appeared during the course of this study.⁶⁻⁸ These will be discussed in more detail later.

MATERIALS AND METHODS

The patients selected for this study in reality constituted two groups, features of which are shown in table 1. The first group represented five patients (cases 1 to 5) who were arbitrarily chosen as examples of moderate to severe hepatitis on the basis of jaundice, anorexia and other symptoms which had been progressive despite bed-rest, a high caloric diet and intravenous glucose infusions, and which were characterized by a total serum bilirubin of 15.0 mg. per cent or higher. It is not implied that these five patients were necessarily entering a phase of acute liver failure or fulminant hepatitis, since we have seen in our Center many cases of similar severity who eventually recovered with or without a prolonged course. It is in this group of patients, however, that a fulminant form of hepatitis may suddenly and unpredictably intervene which usually terminates fatally.

The second group of six patients (cases 6-11) was selected for treatment because of the appearance of certain signs and symptoms we have come to associate with the fatal form of the disease. The most important of these, in our opinion, are an altered state of consciousness and evidence of

* Received for publication March 11, 1953.

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‡ The experience of this center in this form of therapy includes five cases treated by Colbert et al.,¹ four cases included in a report by Eichman et al.,⁴ 30 acute cases treated in controlled studies by us,^{2,3} two cases as yet unreported, and the 11 severe cases in the present paper, one of whom was treated in consultation at another Army hospital because he was too ill to be transferred here.

a rapidly decreasing liver dullness. In this regard, case 5 probably falls between these two groups.

Treatment Schedule and Laboratory Studies: The diet, general management and laboratory studies employed were similar to those previously described.^{2, 3}

The general plan of hormone therapy was to treat the patient until the total serum bilirubin had returned to normal. The dosage schedule employed was as follows: ACTH was given for the first five days by the daily intravenous administration of 10 to 20 mg. in 1,000 ml. of 5 per cent glucose in distilled water. The solution was allowed to run in slowly over an eight hour period. After five days intramuscular therapy was substituted, starting usually with 80 mg. daily. In other patients cortisone was given intramuscularly in doses of 100 mg. every eight hours the first day,

TABLE I

Characteristics of Patients with Viral Hepatitis at the Start of ACTH or Cortisone Therapy

Patient No.	Age	Day of Illness	TSB (mg. %)	1'SB (mg. %)	Chol. Esters in Per Cent of Total	Decreasing Liver Size	Fetor Hepaticus	State of Consciousness	Bleeding Tendencies
1	23	19	23.70	11.30	25	No	No	Normal	No
2	23	21	17.10	8.96	39	No	No	Normal	No
3	20	23	26.44	12.01	36	No	No	Normal	No
4	23	26	24.00	10.80	27	No	1+	Normal	No
5	23	49	57.08	34.10	9	Yes	? Yes	Drowsy	No
6*	32	20	17.40	7.14	—	Yes	3+	Delirious	No
7*	37	28	22.60	10.80	30	Yes	2+	Stuporous	No
8*	22	30	28.60	13.22	11	Yes	2+	Drowsy	Yes
9*	23	41	19.60	7.0	57	Yes	3+	Drowsy	Yes
10*	21	31	32.8	13.5	27	Yes	Unknown	Early coma	Yes
11*	30	14	18.4	8.50	42	Yes	? Yes	Coma	No

* Fatal cases.

TSB—Total serum bilirubin.

1'SB—1 minute serum bilirubin.

every 12 hours the second day, and every 24 hours thereafter. A higher dosage schedule was employed in some cases (cases 8 and 9). Both ACTH and cortisone were used in case 8.

Additional therapy was given to cases 6 to 11, in whom evidence of a rapid downward course was seen. It included oxygen therapy, intravenous glucose, levulose and choline and, in some cases, intubation with a duodenal tube for feeding purposes. Cardiac "stimulants," endotracheal intubation and positive pressure oxygen were administered terminally in fatal cases that developed cardiopulmonary complications. Penicillin instead of aureomycin was given in the fulminant cases.

Controls: An attempt was made to compare the course of the five surviving cases treated with ACTH or cortisone with untreated cases of similar severity. One hundred forty-seven control cases were selected from our files solely on the basis of peak total serum bilirubin (TSB) values over 15 mg.

per cent. One hundred had values between 15 and 30 mg. per cent, 47 had values between 31 and 51 mg. per cent. Obviously, too many other factors are involved to make comparisons of this type in other than very general terms, but these cases are included for purposes of orientation in the average course of this type of case.

RESULTS

The effect of ACTH and/or cortisone on the course of severe hepatitis is best reported by separate consideration of the nonfatal cases (1 to 5) and the fatal cases (6 to 11).

TABLE II
Results of ACTH and Cortisone Therapy in Five Cases of Severe Hepatitis
as Compared with 147 Controls

Group and Patient No.	Highest TSB		Day of Illness when Test Returned to Normal*	
	Value	Day of Disease	TSB (1.00 or less)	BSP (10% or less)
Treated				
1	23.7	19	101	74
2	17.1	21	215	215†
3	27.8	25	67	90
4	24.0	26	80	78
5	57.1	49	102	157†
Treated Average	29.9	28.6	113.0	123†
Control Group A	18.0	21	72.0	80.7
Group B	34.6	36	103.9	104.6
Control Average	24.0	25.6	82.5	88.0

* Figures represent day when test returned to normal and stayed there. For example, patient 1 reached a normal TSB initially on 74th day, but had a subsequent rise, then returned permanently to under 1.00 on the 101st day.

† Indicates that test did not return to normal during observation period.

Group A represents 100 cases with a peak TSB between 15.0 and 30.0 mg. %.

Group B represents 47 cases with a peak TSB between 31.0 and 51.0 mg. %.

Nonfatal Cases: Four of these patients received ACTH and one cortisone. The most striking effects of therapy were a consistent and rapid decrease in bilirubinemia and the relief of symptoms, both of which began within the first five days of administration. Such results are in accord with our previous controlled studies of these hormones in viral hepatitis.^{2,3} The day after onset of illness on which the TSB returned to normal and when bromsulfalein retention (BSP) reached 10 per cent or less, is shown in table 2. For purposes of orientation, similar data are shown for the 147 untreated control cases. It is apparent by rough comparison of these figures

that ACTH and cortisone did not accelerate the recovery from illness in terms of these two tests.

The benefits as well as the difficulties of hormonal therapy in the management of such patients are illustrated in the following brief case reports:

CASE REPORTS

Case 1. A 29 year old white male. ACTH was started on the nineteenth day of disease when TSB was 23.7 mg. per cent. There was some symptomatic improvement, and a drop in TSB to 8.70 mg. per cent by the twenty-seventh day of illness. During the next week, on a dosage of 60 mg. daily, patient relapsed, with return of symptoms

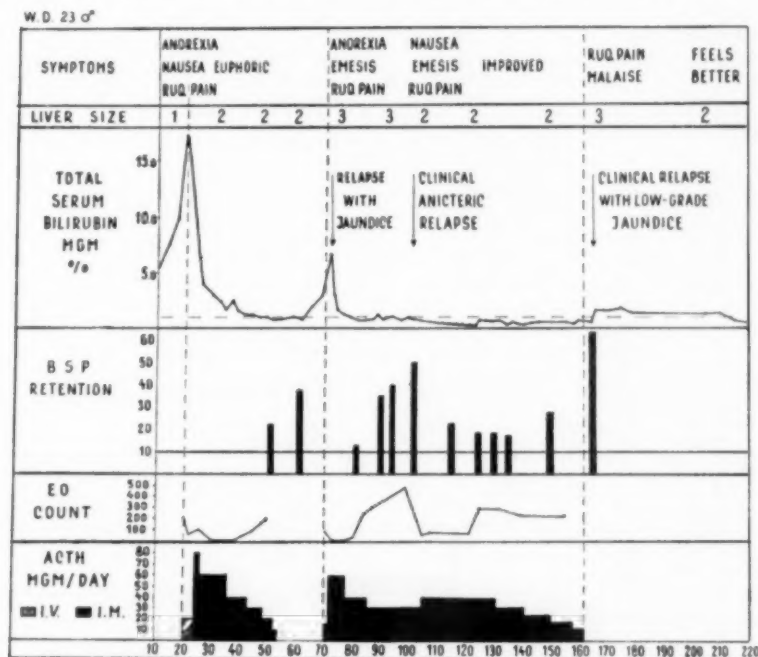


FIG. 1. Course of illness in case 2.

and a rise in TSB to 12.24 mg. per cent by the thirty-second day. Increase in daily dosage to 80 mg. resulted in a second drop in TSB and improvement in symptomatology. A second mild relapse, with symptoms and an increase in TSB from 3.62 to 4.04 mg. per cent occurred with reduction of ACTH to 60 mg., but improvement followed on the same dosage. ACTH was finally discontinued five days after a normal TSB had been reached on the seventy-fourth day of illness and after two months' therapy. A slight rise in TSB to 1.12 mg. per cent occurred about 10 days later, but it spontaneously returned to normal. By the one hundred thirtieth day of illness the patient was asymptomatic, had a normal bromsulfalein retention and was considered ready for discharge to a Reconditioning Center.

Case 2. (Figure 1.) A 23 year old white male. ACTH was started on the twentieth day of illness, when TSB was 17.10 mg. per cent. With the exception of a mild recurrence of symptoms and slight rise in TSB during decrease in dosage from 60 to 40 mg. daily, the response was excellent and the drug was discontinued on the fifty-third day, when the TSB had returned to normal and the BSP retention was 20 per cent. After about 10 days, during which time the patient had some malaise and abdominal cramps, and a rise in BSP retention to 38 per cent, there was a severe clinical relapse, with emesis, right upper quadrant pain and the reappearance of jaundice. ACTH was started again on the seventieth day, when the TSB was 6.5 mg. per cent. Symptomatic improvement and a decrease in clinical jaundice followed rapidly, but clinical symptoms recurred when ACTH was gradually reduced to 30 mg. daily. An increase to 40 mg. daily provided relief from symptoms. After three

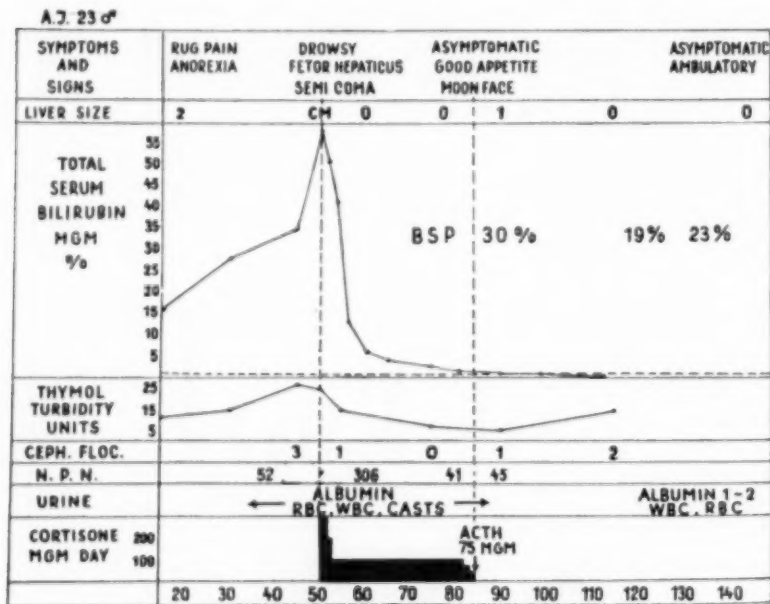


Fig. 2. Course of illness in case 5.

weeks at this increased level, dosage was again dropped to 30 mg., again with complaints from the patient of abdominal distress. Despite this, and with supportive therapy in the form of daily intravenous glucose, ACTH was gradually decreased and finally discontinued on the one hundred sixty-first day of disease, after 123 days of administration. During the period of lowering dosage there was no jaundice but the BSP retention rose from a low of 17.5 to 28 per cent. A liver biopsy done at the time ACTH was discontinued revealed evidence of persistent hepatitis. During the five days following cessation of ACTH therapy, BSP retention further increased, to 63 per cent, and low grade clinical jaundice again appeared, beginning on the one hundred sixty-fifth day of illness. No more ACTH was given but the patient finally returned to a normal TSB on the two hundred fifteenth day of illness. At that time

the patient still had an enlarged and somewhat tender liver. He was believed to have chronic hepatitis and was returned to America for further convalescence.

Case 3. A 20 year old Puerto Rican soldier. ACTH was started on the twenty-third day of illness, when TSB was 26.44 mg. per cent. Symptomatic improvement and a decrease in jaundice occurred without euphoria, and a normal TSB was reached on the sixty-seventh day of illness; ACTH was discontinued on the seventy-seventh day. The BSP reached a value under 10 per cent on the ninetieth day, and the patient was considered ready for discharge to a Reconditioning Center on the hundred and second day.

Case 4. A 23 year old white male. ACTH was started on the twenty-ninth day of disease, when TSB was 24.00 mg. per cent. Appetite improved and TSB dropped to 9.4 mg. per cent by the thirty-sixth day of illness. While receiving 60 mg. per day of ACTH, patient had a mild clinical relapse, with rise in TSB to 10.62 mg. per cent, which responded to an increase in ACTH to 80 mg. daily. Subsequent course of this patient was uneventful and ACTH was discontinued on the eighty-seventh day of illness, after about two months of therapy. No further relapses occurred.

Case 5. (Figure 2.) A 23 year old white male was started on cortisone on the forty-ninth day of illness because of progressive jaundice, drowsiness, abdominal distention and apparent decrease in size of liver. The TSB was 57.08 mg. per cent; cholesterol esters, 21 mg./100 (9 per cent of total), and the urine revealed 3 to 4 plus albumin, with red cells, white cells and casts. A duodenal tube was inserted through which a high caloric liquid diet, with added methionine and choline, was given. On the second day of cortisone therapy the patient became more alert but was otherwise unchanged. During the next two days he became drowsier and developed abdominal pain, and Kussmaul's respirations appeared. The nonprotein nitrogen rose to 164 mg. per cent and the urea nitrogen to 50 mg. per cent. The CO_2 combining power was 29 vol. per cent. Patient was placed in an oxygen tent and $\frac{1}{2}$ molar Na lactate was given intravenously. Following 500 ml. of the lactate solution marked improvement was seen, and on the next day the patient ate well enough to allow removal of duodenal tube. Jaundice decreased rapidly in the next few days to 12.6 mg. per cent, and after reaching a peak level of 306 mg. per cent the nonprotein nitrogen also returned slowly to normal. The subsequent course of this patient was uneventful, and cortisone was discontinued after 37 days' administration. After 157 days of illness the patient, although asymptomatic, still had bromsulfalein retention of 19 per cent, thymol turbidity of 15.5 units and a 2 plus cephalin flocculation.

COMMENT

It is apparent from the case reports above that relapses, of both major and minor severity, and frequently multiple in the same patient, were a serious problem in the management of three of these five patients. Not only did relapses occur on discontinuance of ACTH therapy, but also minor episodes of this type were seen on decreasing the daily dosage as little as 10 mg. Single relapses are very uncommon at this Center in patients not receiving hormonal therapy, with an incidence under 1 per cent in some 3,000 previously studied patients,⁵ and multiple relapses as seen with ACTH are rare indeed. The prolonged, relapsing type of illness, such as that in case 2, suggests that ACTH may have adversely affected the total course of illness, leaving the patient with protracted if not chronic hepatitis. The

influence of cortisone on the complicated course of case 5 is difficult to evaluate, since the part played by renal involvement and its attendant acidosis in the clinical picture is unknown. The severity of the jaundice, the evidence of decreasing liver size and the presence of drowsiness point to the start of acute hepatic failure, in which the prognosis is indeed very grave. When definite coma intervenes in such patients, the outcome has been almost

TABLE III
Data on Six Fatal Cases of Viral Hepatitis Treated with ACTH and/or Cortisone

Patient No.	Hormone Therapy			Day† Coma Started	Day† of Death	Result of Therapy	Autopsy Findings	
	Type	Total Amount and Route	Day† Started				Weight of Liver	Pathologic Diagnosis*
6	ACTH	Mg. 50 IV	20	19	21	None	Gm. 800	(1) Acute yellow atrophy of liver. (2) Toxic nephrosis.
7	ACTH	20 IV 100 IM	28	28	30	None	750	(1) Hepatic necrosis, massive. (2) Cholemic nephrosis. (3) Pulmonary atelectasis.
8	ACTH Cortisone	70 IV 800 IM	30 32	32	34	None	1200	(1) Hepatic necrosis, severe. (2) Bronchopneumonia.
9	Cortisone	4050 IM	41	48	61	Transient decrease in jaundice with symptomatic improvement.	1000	(1) Infectious hepatitis, massive liver necrosis.
10	ACTH	180 IM	31	31	33	None	1300	(1) Hepatic necrosis, massive
11	ACTH	700 IM	14	13	22	None	N.R.	(1) Hepatic necrosis, massive.

IV = Intravenous. IM = Intramuscular. NR = Not recorded. * The diagnoses of liver disease given by different pathologists are all synonyms for the same condition in acute hepatic necrosis. † Day refers to day of disease.

invariably fatal. Thus, the implication is strong that cortisone was a significant if not major factor in the recovery of this case.

Fatal Cases: Features of these cases are given in table 1. All had evidence of acute or subacute hepatic failure. In four of the six cases, hepatic coma occurred about the day hormonal therapy was started; in the fifth case two days later, and in the sixth case one week later. The results of therapy and length of survival are shown in table 3. Three patients (cases 6, 7 and 10) had a very rapid terminal course and died within two days of the start

of therapy. In none of these was there any observable effect of hormonal therapy except eosinopenia. Case 11 lived eight days after ACTH was started, but was in deep coma and maintained only in a respirator during this period. Case 8 developed coma on the second day of hormonal therapy and died two days later. Neither of these two cases showed any clinical response. Case 9 died 20 days after cortisone therapy was instituted, and in this patient a transient clinical improvement occurred, accompanied by a drop in serum bilirubin. A brief report of this patient is given below:

T.W. 23 ♂ NEGRO

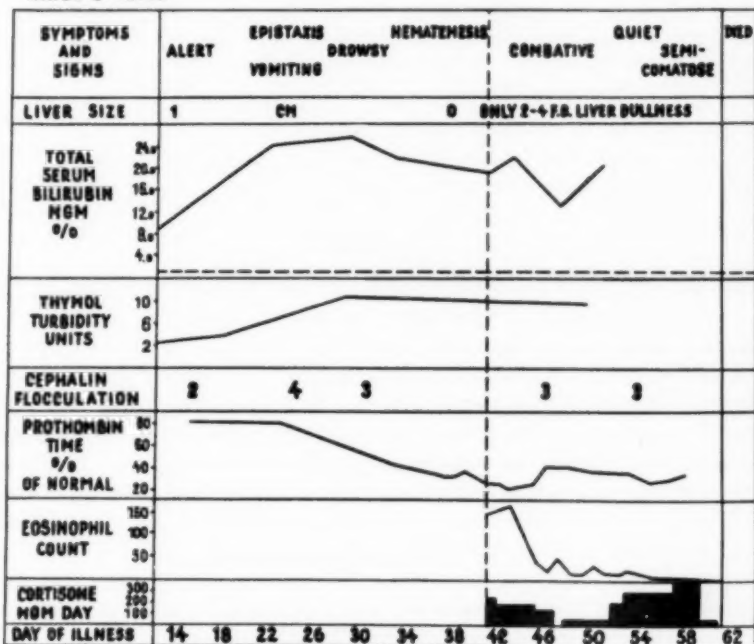


FIG. 3. Course of illness in case 9.

Case 9. (Figure 3.)* A 23 year old colored soldier. Started on cortisone on forty-first day of illness because course had been characterized by progressive jaundice, hypoprothrombinemia with bleeding from nose, gums and intestinal tract, including an episode of hematemesis of 120 ml. of bright red blood, severe abdominal pain and drowsiness. Fetus hepaticus and a decreasing liver size had been noted. The TSB was 19.6 mg. per cent and urea nitrogen was 10.3 mg. per cent. Prior treatment had consisted of intravenous glucose, blood transfusions, vitamin K and bed-rest.

For four days following commencement of cortisone, the patient became more alert and evidenced some appetite, and his jaundice lessened. However, on the fifth

* This patient was seen in consultation at the 5th General Hospital, USAREUR, and is reported through the kind permission of Col. Henry N. Greenleaf, Chief of Medical Service, and with the assistance of Lt. Vergil Place, M.C.

day of treatment he became irrational and combative, and this progressed to delirium and stupor. Cortisone was reduced and then interdicted temporarily because it was feared it might have been responsible for the mental change. No improvement was seen, however, and cortisone was started again at a daily dosage of 300 mg. The patient became a little less difficult to handle but remained incontinent of urine and feces. This condition persisted essentially unchanged for a week while he was still on high doses of cortisone, and then he became more deeply comatose; fever, tachycardia and a shocklike state developed, and the patient died.

COMMENT

The failure of hormonal therapy to alter the course of disease in five of the six fatal cases might be attributable to the fact that therapy was begun too late and that the rapidity of the terminal course was too great to reverse. However, the onset of the fulminant phase was often so abrupt that it would have been difficult to diagnose earlier. In one case in which the tempo of the process appeared to be less rapid, hormone therapy produced no more than fleeting clinical improvement.

DISCUSSION

The present report has been concerned primarily with the use of ACTH and cortisone in severe and fulminant cases of viral hepatitis. In five severe cases, each with a serum bilirubin over 15 mg. per cent, there was a prompt initial fall in serum bilirubin, accompanied by symptomatic improvement following institution of hormonal therapy. One case went on to uneventful recovery; one case in which treatment may have been life-saving was left with persistent evidence of elevated bromsulfalein retention, and the other three cases experienced multiple relapses associated with this therapy, from which two eventually recovered and one was left with chronic hepatitis. These results are in general accord with those of Rifkin et al.,⁶ who treated four severe cases of serum hepatitis with cortisone or ACTH. In these symptomatic relief was produced, but two cases relapsed at the end of hormone therapy, and one went on to chronic hepatitis.

Six cases of fulminant hepatitis who were started on treatment with ACTH and/or cortisone when there was definite evidence of acute liver decompensation, with actual or impending coma, all pursued an essentially unaltered course to death. In five of these cases the terminal phase proceeded so rapidly that it may be questioned whether these hormones, even if effective, had sufficient time to produce a result. This criticism cannot be made in one fatal case, in which cortisone was started two weeks prior to death. In this patient only transient benefit was seen. It is our impression that when evidence of coma and a rapidly shrinking liver appears in patients with viral hepatitis, a "point of no return" has been reached in which hepatic necrosis is so severe and progressive that usually no therapy will

avail. Experience with large numbers of hepatitis patients reveals a fair percentage of cases who develop a severe form of the disease, some of whom may have signs suggestive of *impending* coma. These patients often recover and should not be confused with true hepatic coma in the evaluation of clinical results with adrenal cortical hormones. However, the recovery of two patients in actual hepatic coma has been reported by Ducci and Katz,⁷ who used very large doses of cortisone plus antibiotics; but three other similarly treated comatose patients, with more chronic forms of hepatitis, did not survive. Wildhirt⁸ has also claimed the recovery of three of six patients in hepatic coma by the intravenous administration of adrenal extract, levulose and choline. These two reports are not in accord with our experience, but we have not used exactly the same treatment schedule as these authors. Almost any therapeutic effort would seem justifiable under such desperate circumstances as the comatose hepatitis patient presents.

Our experience with adrenal cortical hormones in the 11 cases of viral hepatitis reported in this paper, plus 36 other patients reported in separate papers^{2, 3, 4} may be summarized as follows:

The administration of cortisone or ACTH has been shown capable of inducing a marked and often dramatic drop in the intensity of jaundice. This has been demonstrated by greater decreases in serum bilirubin than were seen in similar patients not receiving these hormones. The effect on other liver function tests has been variable, but there is suggestive evidence of a more rapid return of bromsulfalein retention to normal. The total duration of apparent illness in patients receiving cortisone and, under certain conditions, those receiving ACTH has been significantly shorter than in patients of the control groups. Furthermore, cortisone-treated patients have shown a consistently more rapid tendency toward histologic healing in liver biopsy specimens than have patients of the control group. These benefits of hormone therapy have been sharply limited by a relapse rate of about 25 per cent with either ACTH or cortisone. The frequency of such relapses seems to be greater in the patient with severe hepatitis. Other serious limitations to the use of these hormones have been the frequency of side reactions, their failure in preventing chronic hepatitis and, finally, their inability in our experience to reverse the course of fulminant hepatitis with coma.

The effect of these hormones on the actual clinical course and manifestations of viral hepatitis has been at times as striking as the results reported in rheumatic fever and rheumatoid arthritis. Unlike these diseases, however, hepatitis is usually a benign and self-limited disease accompanied by adequate immunity. With the high relapse rate attending ACTH and cortisone therapy in hepatitis, which may reflect actual interference in mechanisms important in immunity, the routine use of hormone therapy in viral hepatitis does not seem indicated.

SUMMARY

ACTH and/or cortisone has been used in the treatment of 11 cases of viral hepatitis, five of whom were moderately to severely ill and six of whom had a fulminant course with coma. In the first group, hormone therapy was associated with symptomatic control and a drop in serum bilirubin, but in three of the five cases relapses of both major and minor severity occurred, and multiple relapses were observed in the same patient. In the second group all six cases died, and no significant benefits of hormonal therapy were seen.

A brief discussion of our total experience with these compounds in hepatitis is given.

ADDENDUM

Opportunity to treat a case of fulminant hepatitis with a schedule like that of Ducci and Katz² has recently been given one of us at the University of Wisconsin Student Infirmary. This occurred in a 22 year old Chinese male under streptomycin and Marsilid therapy for minimal pulmonary tuberculosis. When jaundice was noted, all medication was stopped and a high protein and carbohydrate diet was instituted. Three weeks later, his jaundice became quite suddenly more marked, he became disoriented, and his liver began to decrease in size. Total and direct serum bilirubin were 44 and 25 mg. per cent, respectively. At this time, intramuscular cortisone was started in total daily dosage of 1,000 mg., and 1,000 mg. of aureomycin were given intravenously daily in 15 per cent glucose. This same schedule was given daily until the patient's death three days later. During this period there was no observable response to therapy: coma became progressively deeper, the liver smaller, grand mal seizures appeared, and the patient died in pulmonary edema.

A 26 year old female with fulminant serum hepatitis has also been treated at the 98th U. S. Army General Hospital since the completion of this manuscript. Definite coma and a small liver were present at the institution of therapy with 1,000 mg. of cortisone daily, intravenous levulose and choline, and prophylactic penicillin. In this instance, recovery ensued after 19 days of cortisone therapy and after a 48 hour period in hepatic coma. Cortisone certainly deserves further trial in this type of case.

ACKNOWLEDGMENT

Acknowledgment is made to Maj. General Guy B. Denit, Chief Surgeon, USAREUR, for his continuous interest and encouragement in this work; to Colonel Emery E. Ailing, William S. George and James D. Gardner, of the 98th General Hospital, for their active support, and to the following physicians of the Hepatitis Section for their assistance: Lieutenant Morton N. Swartz, Captain John W. Callister, Dr. Guenter Blume and Dr. Karl-Heinz Ronde. We also wish to thank Mrs. Mara Iwan for clerical help.

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RENAL DISEASE WITH THE SALT LOSING SYNDROME: A REPORT OF FOUR CASES OF SO-CALLED "SALT LOSING NEPHRITIS" *

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CHRONIC renal insufficiency produced by any progressive disease of the kidney may be associated with a variety of complications. Traditionally, it is known that diseased kidneys fail to excrete nitrogenous substances, and that this retention leads to azotemia and uremia. While the retention of salt and water by the kidney is considered the main cause of edema, any progressive kidney disease, whether polycystic kidney, chronic glomerulonephritis, tuberculosis of the kidney or pyelonephritis, may become associated not only with retention but also with excessive depletion of certain essential substances.

For some years the significance of abnormally low serum electrolytes has been known and the clinical features have been recognized. Within recent years the importance of the tendency to excessive sodium loss in chronic renal disease has attracted considerable attention. However, not only may chronic renal diseases cause this salt losing tendency, but it may appear also in acute renal disease such as acute toxic nephrosis.^{1, 2} In all cases there is unanimity of opinion that the tubules are disordered and fail to conserve sodium chloride in a normal manner, and the importance of hyponatremia in chronic renal insufficiency and its influence on uremia have been recognized for some time. Peters, Wakeman, Eisenman and Lee,³ Peters, Wakeman and Lee,⁴ Peters and Van Slyke,⁵ and Landis, Elsom, Bott and Shiels⁶ were among the investigators to describe hyponatremia and dehydration during uremia in patients without edema. More recently Thorn, Koepf and Clinton⁷ published an impressive article on renal failure simulating adrenal cortical insufficiency. In this article they pointed out that, in addition to the hyponatremia and dehydration without edema, the shocklike state simulating acute adrenal insufficiency was also present. For this syndrome they introduced the term "salt losing nephritis." This article stimulated the interest of clinicians, pathologists and physiologists alike, and subsequent investigations have resulted. Following the report of their two cases, other articles on the subject made their appearance.⁸⁻¹² At the present time eight cases have been reported in the literature.

It is our desire to present four more cases of renal disease which exhibit the salt losing syndrome and which simulate cases already reported. Our

* Received for publication November 25, 1952.

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Presented at the Midwest Regional Meeting of the American College of Physicians, Chicago, Illinois, November 22, 1952.

purpose is to emphasize the need for early recognition of salt depletion syndrome in chronic renal disease, as adequate treatment is followed by most gratifying therapeutic results; to stress that not all patients with so-called "salt losing nephritis" present the advanced picture of Addison's disease, as this is only an extreme example of failure of the kidney to conserve salt; to alert others to this complication in these days of salt restriction and the use of measures which eliminate the minerals from the body; and to stimulate further investigation of the nature of the pathologic-physiologic process of the tubular system during disease.

CASE REPORTS

Case 1. First Admission:* A 35 year old married white male was first seen on July 14, 1949. He had been refused life insurance because of the presence of albuminuria, and a diagnosis of chronic nephritis had been made. At this time he was

TABLE I
Features of Salt Losing Nephritis
H.H. (35 year old white male)

Date	Blood				Urine			B.P.	Comments
	Na mEq/L	Cl mEq/L	NPN	CO ₂	S.G.	Volume	Cl mEq/L		
8-29-49	138.0	99.0	143.0	24.5	1.005	2400	—	140/100	Chronic glomerulonephritis. Alb. 1-2+. No casts.
1949-1951	—	—	163.0	26.0	1.008	1800	—	120/92	Studied at other institutions. Above diagnosis confirmed.
10-22-51	122.0	80.0	150.0	22.5	1.006	2200	—	120/80	Alb. 1-2+. No casts. Weak, pain in the legs, nausea. Diagnosis: Salt depletion.
12-18-51	118.0	86.0	187.0	30.5	1.004	1200	248.0	90/50	Muscle cramps in legs almost unbearable. Impending uremia. Muttering, delirium, state of collapse. Diagnosis: salt losing nephritis. 10 gm. sodium chloride and 10 gm. sodium bicarbonate orally.
2-26-52	135.0	98.0	70.0	32.0	1.006	1200-2500	262.0	130/90	Comfortable. Ambulatory and apparently normal.
9-20-52	142.0	102.0	68.0	38.0	1.008	—	—	136/100	Comfortable but not working.

not disabled and was working steadily. The family history was unimportant. Past history showed he had been discharged from the Army in 1945, apparently in normal physical condition, although he had had repeated attacks of acute streptococcal sore throat. In 1947 he first learned of the presence of albuminuria, but it was not until July, 1949, that he began to feel tired and "run down." He was admitted to the hospital on August 29, 1949.

Physical Examination: This revealed a thin, leathery appearing individual who had no complaints except those of weakness, anorexia and general malaise. The blood pressure on admission was 140/90 mm. of Hg. The ophthalmoscopic examination showed no abnormalities. The nose and throat were normal. Tonsils had been removed. No lymph nodes were palpable in the neck. The lungs were clear to auscultation and percussion. The heart was normal. There was no edema.

Laboratory Examination: The urine showed a trace of albumin and occasional white and red blood cells. The specific gravity was 1.005. Measured daily urine

* See table 1.

excretion ranged from 1,800 to 2,600 c.c. The hemoglobin was 70 per cent, and there were 3,570,000 red blood cells. Blood chemistry values were as follows: nonprotein nitrogen, 143 mg. per cent; urea nitrogen, 78 mg. per cent; total protein, 6.1 gm. per cent (albumin, 3.6 gm. per cent; globulin, 2.5 gm. per cent). Renal function studies revealed the following: dilution concentration test a range in specific gravity from 1.008 to 1.018; phenolsulfonphthalein excretion in two hours of 22.4 per cent; and urea clearance of 45.1 per cent of normal.

Course in the Hospital: The patient was discharged from the hospital with a diagnosis of chronic glomerulonephritis. During the following two years, in his effort to obtain a more favorable diagnosis and prognosis, he was seen at several other clinics. Diagnosis made elsewhere was the same: chronic glomerulonephritis.

Second Admission: On October 22, 1951, he reentered the hospital because of generalized weakness, fatigue and, particularly, extreme weakness and severe pain in the legs.

Physical Examination: There was little change in the general condition of the patient. The blood pressure, however, had dropped to 120/80 mm. of Hg, and the patient was slightly dehydrated.

Laboratory Examination: Urine examination was essentially unchanged: a low specific gravity of 1.006; albumin, 1 plus; occasional red cells; no sugar, and no casts. Blood chemistry values were as follows: nonprotein nitrogen, 150 mg. per cent; urea nitrogen, 74 mg. per cent; and total protein, 8.4 mg. per cent (albumin, 5.8 gm. per cent, and globulin, 2.6 gm. per cent). The sodium was 122.0 mEq./L. and the chloride was 80 mEq./L. The CO_2 combining power was 22.5 mEq./L.

Course in the Hospital: On November 8 the patient left the hospital, although there was very little objective improvement.

Third Admission: On December 18, 1951, the patient was re-admitted to the hospital in a state of impending uremic coma. Muscle cramps of the legs had become worse; he was vomiting and was continually nauseated.

Physical Examination: The patient was covered with a cold sweat; the pulse was weak and rapid, and the blood pressure had dropped to 90/50 mm. of Hg. Aside from these changes, his condition was essentially the same as on the previous admission.

Laboratory Examination: Urinary output ranged from 1,200 to 2,500 c.c. a day, with a specific gravity of about 1.004. The hemoglobin concentration was 58 per cent, and there were 2,330,000 red blood cells. Blood chemistry values revealed a nonprotein nitrogen of 187.0 mg. per cent, urea nitrogen of 103.8 mg. per cent, CO_2 combining power of 30.5 mEq./L., sodium of 118.0 mEq./L., and chloride of 86.0 mEq./L. An electrocardiogram at this time showed a sinus tachycardia.

Course in the Hospital: It was at this time that the clinical picture simulated cases of salt losing nephritis, and subsequently 24 hour urinary excretion of sodium chloride was found to be 13.4 gm. per 24 hours. An intravenous pyelogram of the kidneys revealed shrunken kidneys, with no dye appearing at any time in a period of over 30 minutes. A diagnosis of chronic nephritis of the salt losing type was made. Treatment consisted of 1,000 c.c. of 1/6 molar sodium lactate solution and 1,000 c.c. of physiologic saline solution daily. The vomiting stopped and the nonprotein nitrogen, which had risen to 266.6 mg. per cent, gradually dropped to 87 mg. per cent. The output of urine remained high, the specific gravity low. The patient became stronger and more alert, and the presenting symptomatology disappeared. He was placed on a daily regime of 10 gm. of sodium chloride and 5 gm. of sodium bicarbonate orally. Discontinuance or reduction in the intake of sodium chloride and sodium bicarbonate resulted in return of nausea and weakness, listlessness and painful legs.

Because many of these patients had been considered to be suffering from Addison's disease or related to adrenal insufficiency, this patient was given a therapeutic trial with cortisone, without benefit.

On his discharge from the hospital the following observations were made: the blood pressure had risen to 140/90 mm. of Hg; the blood nonprotein nitrogen was 78.9 mg. per cent; the sodium was 135 mEq./L., the chlorides were 98 mEq./L., and the potassium was 6.3 mEq./L.

Follow-up: Since leaving the hospital, the patient has been seen at frequent intervals, and the blood nonprotein nitrogen has remained at levels of about 70 mg. per cent. The sodium and the chlorides of the serum are practically normal. Nausea and vomiting have been controlled, and the pain and weakness of the legs have not recurred. While he has not recovered from his chronic glomerulonephritis, he has overcome, at least for the time being, the symptoms and signs generated by the loss of sodium chloride.

The patient was last seen on September 20, 1952. He is ambulatory but continues to have chronic renal insufficiency.

Case 2. First Admission:* A 53 year old white male entered the hospital on June 27, 1949, complaining of pain in the left hip of four years' duration. Except for intermittent epigastric pain of seven years' duration, the patient had been quite well.

TABLE II
Features of Salt Losing Nephritis
W.R. (53 year old white male)

Date	Blood				Urine			B.P.	Comments
	Na mEq./L.	Cl mEq./L.	NPN	CO ₂	S.G.	Volume	Cl mEq./L.		
9-13-49	115.7	81.7	96.4	25.8	1.010	1.070	125.3	70/46	Confused, disoriented, hallucinating. Alb. 2+. Casts 0. RBC 0.
9-21-49	123.1	91.0	106.2	22.8	1.011	1.110	143.6	82/60	Weakness, periodic confusion.
9-30-49	125.4	97.6	96.0	—	1.010	2.020	202.1	80/45	Weakness, Wilder test neg. Mentally clear.
10-18-49	132.6	86.9	63.0	34.0	1.011	3.080	172.4	—	Weakness. NaCl 6 gm. orally every day.
11-8-49	136.1	86.2	78.8	27.9	1.011	1.505	68.7	90/60	Strength improving. Regular diet and NaCl, 2 gm. daily.
3-27-50	—	89.6	85.0	—	1.010	—	—	94/60	Feels well.

About eight months prior to admission he injured his right elbow, following which he had had pain and swelling in the elbow which seemed out of proportion to the injury. Shortly following this the patient had a series of migratory joint pains lasting for from one to two weeks.

Four weeks prior to admission his right shoulder had become extremely painful and disabled. Aspiration by a private physician yielded a large amount of creamy material. The joint symptoms disappeared following this procedure. Four days prior to admission the patient developed similar moderately severe pain in the left hip, and he was hospitalized.

It was further learned that in 1946 the patient had been hospitalized elsewhere and a diagnosis of peptic ulcer had been made. He had been taking alkaline powder for the past few years, consuming a large bottle every two weeks. Also, he had been hospitalized in another hospital in 1948 because of a "kidney infection" and "albumin in the urine." He had been treated with parenteral fluids and "the infection cleared up."

System review revealed generalized weakness of six months' duration and nocturnal vertigo for the past four weeks. He had lost 20 pounds in the last six years.

* See table 2 and figure 1.

Physical Examination: The patient was a well developed, well nourished white male who was pallid but did not appear ill. The temperature was normal. The head was negative. Ophthalmoscopic examination was negative. The lungs were clear. The heart was not enlarged. The rhythm was regular, and there were no murmurs. The blood pressure was 90/60 mm. of Hg. The abdomen was negative. The left hip was painful on abduction and adduction, markedly tender to pressure and mildly warm to touch. There was no edema.

Laboratory Examination: The urinary volume varied from 1,800 to 3,500 c.c. a day. The specific gravity was 1.003. There was no albumin or red blood cells and only an occasional white cell. The hemoglobin was 78 per cent; the red blood count was 3,900,000. The serology was negative. The sedimentation rate was 127/132 mm.

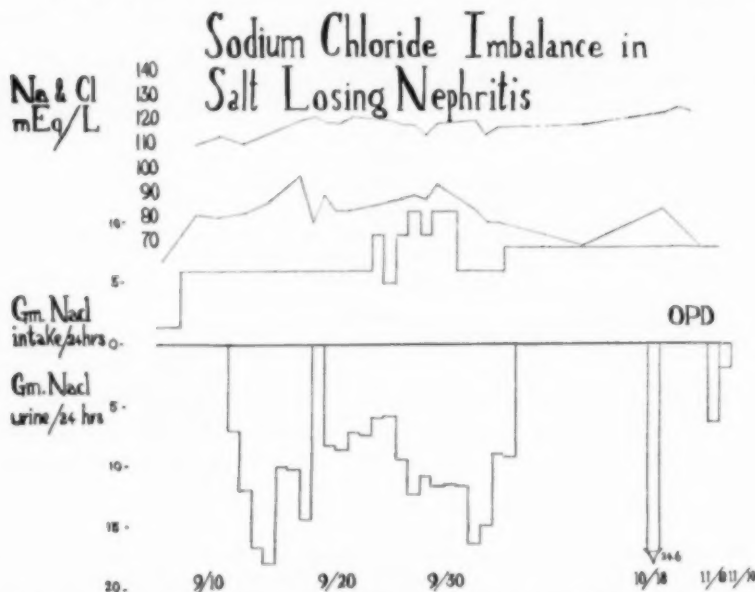


FIG. 1. Case 2. This diagram shows excessive loss of sodium chloride in the presence of a controlled intake of salt. The sodium and chloride mEq./L. of the serum are shown in the upper part of the diagram. Despite a controlled intake of 6 gm. of sodium chloride daily, the patient consistently had a low serum sodium and chlorides and was losing excessive amounts of salt in the urine.

Blood chemistry values were as follows: blood nonprotein nitrogen, 142.8 mg. per cent; chlorides, 55.0 mEq./L. (reported as NaCl); and the alkali reserve, 24.5 mEq./L. X-ray examination of the chest was negative. The electrocardiogram was within normal limits.

Course in the Hospital: Except for weakness, the patient improved without specific treatment. With the withdrawal of alkaline powder during his hospital stay the nonprotein nitrogen dropped to 69.7 mg. per cent and the alkali reserve to 18.4 mEq./L., and the chlorides rose to 74.0 mEq./L. The patient left the hospital on July 14, 1949, before additional studies could be done.

Second Admission: The patient reentered the hospital on August 16, 1949, in a totally disoriented and confused state.

Physical Examination: Temperature was normal; pulse, 84; respirations, 18. The lungs were clear and the heart was normal. Blood pressure was 110/70 mm. of Hg. Rectal examination revealed tarry stool present. Shortly after admission the patient became hyperactive, hallucinating and screaming, which necessitated his transfer to a psychiatric ward. A diagnosis of bleeding peptic ulcer was made which was subsequently proved by x-ray.

Laboratory Examination: Urinalysis revealed a specific gravity of 1.002; pH was 6.0. The hemoglobin was 71 per cent. There were albuminuria of 4 plus and many white blood cells, occasional red blood cells, and no casts. The blood chemistry values were as follows: nonprotein nitrogen, 68.9 mg. per cent; blood urea nitrogen, 43.1 mg. per cent; chlorides, 62.0 mEq./L., and alkali reserve, 33.4 mEq./L. The Addis count on repeat occasions showed as many as 4,740,000 red blood cells, 1,842,000 white blood cells, and 47,000 hyaline casts. The concentration test showed 1.009 and a dilution of 1.002. The phenolsulfonphthalein test revealed 7.5 per cent excretion in one hour.

Course in the Hospital: The patient presented a confused, disoriented mental condition with active hallucinations, and was admitted to the psychiatric ward. He

TABLE III
Features of Salt Losing Nephritis
E.Z. (27 year old white male)

Date	Blood				Urine			B.P.	Comments
	Na mEq./L.	Cl mEq./L.	NPN	CO ₂	S.G.	Volume	Cl mEq./L.		
3- 1-51	140.0	97.1	189.5	17.7	1.012	1.870	90.2	180/110	Nausea, Emesis. Alb. 3+. Casts 0. RBC and WBC occ. Albuminuric retinitis.
3- 6-51	124.5	90.9	162.0	19.7	1.010	1.905	148.3	150/120	Weakness, confusion. IV saline solutions to supple- ment diet.
3-15-51	139.3	92.3	80.0	27.9	1.007	2.590	—	—	Lethargic.
3-20-51	135.6	96.4	127.0	23.7	1.009	1.915	62.7	230/150	Tremulous, slight lethargy*.
4- 5-51	124.3	86.2	98.8	17.4	1.007	2.010	79.3	150/100	Weakness, hiccuping. Diag- nosis: Salt losing nephritis.
4- 9-51	116.9	82.8	96.0	18.9	1.008	1.420	48.9	—	Hiccuping, emesis.
4-12-51	120.0	89.6	98.0	17.5	1.007	1.885	68.4	140/98	Confused. Died. Autopsy. Diagnosis: Chronic glomer- ular nephritis.

* 3-31-51: RBF 24.3; RPF 18.953; GFR 6.52.

was found to have a bleeding peptic ulcer. The blood pressure fell to 96/66 mm. of Hg and remained at this approximate level the rest of his hospital stay. Following a brief episode of oliguria the urinary output became normal in volume. He was treated symptomatically and with intravenous saline. Evidence of bleeding had stopped, and the patient became mentally clear within three days. From September 2 to September 6 he received five liters of normal saline.

Balance studies revealed that the serum sodium varied between 112.2 mEq./L. and 126.2 mEq./L., the serum potassium between 4.17 mEq./L. and 6.93 mEq./L., and the serum chlorides between 72.7 mEq./L. and 90.2 mEq./L., rising to 98.0 mEq./L. on one occasion. During this period the total 24 hour output of NaCl in the urine ran as high as 18.02 gm., and never dropped below 7.0 gm. The balance studies confirmed the fact that, in spite of a daily dietary intake of 6 gm. of NaCl per day, plus supplemental sodium chloride, the patient consistently ran a low serum sodium and serum chlorides, and was losing excessive amounts of salt through the urine. At no time did the patient demonstrate edema clinically. He was given DCA for three days without measured effect on sodium metabolism. On October 5, the blood pressure was 78/40

mm. of Hg. The patient was asymptomatic and was discharged on 6 gm. of oral sodium chloride tablets and an 8 gm. sodium chloride dietary intake, to be followed in the outpatient clinic. The serum sodium at this time was 124 mEq./L. In the outpatient clinic, blood chemistry values repeatedly revealed a moderate nitrogen retention varying between 88.2 mg. per cent and 66.6 mg. per cent; serum chloride from 87.0 to 90 mEq./L., and an alkali reserve of 34.0 to 28.0 mEq./L. Later supplementary sodium chloride was dropped from 6 to 2 gm. daily. He continued to work and was quite comfortable.

Case 3.* A 27 year old white male was admitted for the first time to the hospital on February 25, 1951, complaining of frontal headaches, nervousness and intermittent vomiting of seven days' duration. For the preceding four months he had had increasingly severe "cramping weakness" of both lower legs. One month prior to admission he was found by his private physician to have hypertension, hematuria and albuminuria.

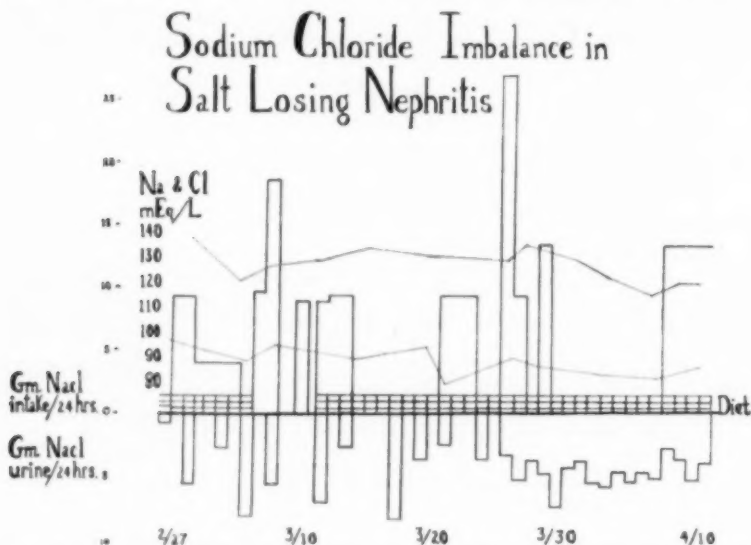


FIG. 2. Case 3. This diagram illustrates that from March 15 to March 31, and from March 31 to April 10, with an intake of sodium chloride of 1.5 to 2.0 gm. daily orally, the output ran from 2.8 to 8.5 gm. During these periods the serum concentrations of sodium fell.

He was apparently well until the age of 21, when he developed a "kidney infection," and for this reason he was subsequently rejected for Army service.

Physical Examination: The patient was a well developed but apparently chronically ill white male who was somewhat sallow and nervous. Temperature, pulse and respirations were normal. Ophthalmoscopic examination revealed minimal papilledema and slightly increased tortuosity of vessels, with grade 3 attenuation and marked A-V nicking. Blood pressure was 210/130 mm. of Hg. The heart was enlarged slightly to the left. P_2 was more intense than A_2 . There were flatness and depressed breath sounds in the right base. Examination was otherwise unremarkable.

Laboratory Examination: The urine showed a specific gravity of 1.005 to 1.018 and a pH of 5-6. Albumin was 3 to 4 plus. Microscopic examination revealed 15 to

* See table 3 and figure 2.

20 red blood cells per high power field and 3 to 4 white blood cells per high power field. The Volhard concentration test showed a specific gravity of 1.011 initially and 1.006 three days before death. The dilution test showed a specific gravity of 1.005 on both occasions. The Addis count revealed 266,000 red blood cells, 66,000 white blood cells and no casts in 12 hours. The hemoglobin was 78 per cent; the red blood cells, 4,270,000. Sedimentation rate was 46 in one hour. Blood chemistry values were as follows: Plasma proteins measured 3.3 gm. albumin and 2.2 gm. globulin; creatinine, 7.0 gm. per cent; nonprotein nitrogen, 142.8 mg. per cent; serum chlorides, 90.9 mEq./L.; CO_2 combining power, 19.7 mEq./L.; serum sodium, 140 mEq./L.; and serum potassium, 8.26 mEq./L.

Course in the Hospital: The patient was placed on a 1.5 gm. sodium chloride diet and bed-rest. The nonprotein nitrogen continued to rise and the serum concentration of sodium began to fall. The brief respite of nausea and vomiting ceased and he symptomatically deteriorated. His urinary output continued between 1,400 and 2,300 c.c. every day, while the urinary excretion of sodium chloride varied from 2.5 gm. to 8.44 gm. daily. The serum sodium dropped to 124 mEq./L. and the chlorides to 86 mEq./L. During a period of observation from March 15 to March 21, and from March 31 to April 10, the intake of sodium chloride was 1.5 to 2.0 gm. a day and the output ran consistently from 2.8 to 8.5 gm. During these periods the serum sodium consistently fell until parenteral sodium chloride therapy was reinstituted. During these periods of stress the kidney was unable to hold on to sodium chloride despite falling serum levels. A diagnosis of salt losing nephritis was made.

The persistently elevated serum potassium was treated with intravenous infusions of 10 per cent glucose with insulin, and the abnormally low serum sodium was treated with isotonic and 3 per cent saline. Sodium increased to 139 mEq./L. and chlorides to 92 mEq./L. The blood pressure at this time was 150/100 mm. of Hg.

A few days later the patient began vomiting again; the nonprotein nitrogen gradually rose to 98 mg. per cent and the sodium fell to 116 mEq./L. Following the intravenous infusion of a liter of 3 per cent saline two months after admission, the patient suddenly developed acute left failure and died.

Autopsy Findings: At autopsy the heart weighed 400 gm. The myocardium was a pale glistening brown. The left ventricle measured 19 mm. and the right ventricle measured 5 mm. The mitral valve measured 10 cm., the tricuspid valve 12 cm., the pulmonary valve 8.5 cm., and the aortic valve 7 cm. The valve leaflets were free and thin. There were slight thickening and rolling of the edges of the mitral valve leaflets. There were plaques present in both the right and left coronary arteries. The aorta was normal.

The left kidney measured 9 by 4 by 3 cm. and weighed 70 gm. The capsule stripped with slight difficulty. The kidney was soft and mushy to the touch. The surface was granular, with several yellowish spots present on the surface. The parenchyma measured 10 mm. and the cortex measured 4 mm. The pelvis and ureter showed a pale, normal appearing mucosa. The right kidney measured 9 by 3 by 2 cm. and weighed 60 gm.; it was similar in appearance to the left. The parenchyma measured 12 mm. and the cortex measured 5 mm.

The adrenals appeared normal except for slight nodular hyperplasia of the cortices.

Microscopically, the kidneys showed that many glomerular tufts were completely hyalinized. Many other glomeruli showed early hyaline changes. Most of the proximal tubules were distended with eosinophilic staining, homogeneous material, and the cells lining these tubules were flattened. A few proximal tubules were present which showed cellular regeneration. The cells of the distal tubules showed degeneration as evidenced by swelling of the cells and loss of nuclei and cellular borders. There was extensive fibrotic infiltration throughout the sections, with aggregates of lympho-

cytes in these areas. There was hyalinization of the afferent arterioles, and most of the blood vessels were congested with red cells.

Case 4.* A 25 year old white male entered the hospital for the first time in October, 1951, with the complaints of nonproductive cough, gradually increasing dyspnea, ankle edema and generalized weakness of about 10 days' duration. The day before admission he had had severe chills and fever.

Since the age of five years he had had "leakage of the heart." In August, 1951, he had had an attack of acute rheumatic fever, after which he had not felt well. There was never a history of renal disease.

Physical Examination: The patient was a well developed, pallid and somewhat apprehensive white male. He was moderately dyspneic at bed-rest. There were several petechiae in the right conjunctival sac. Moist râles and depressed breath sounds were present in both bases. The heart was enlarged to the left and regular in rhythm. There was a grade 3 apical systolic murmur and a mid-diastolic murmur with a presystolic accentuation. The liver was palpable four fingerbreadths in the right midclavicular line and was tender. The tip of the spleen was palpable. Temperature was 102° rectally; pulse, 110; respirations, 28.

TABLE IV
Features of Salt Losing Nephritis
E.S. (25 year old white male)

Date	Blood				Urine			B.P.	Comments
	Na mEq./L.	Cl mEq./L.	NPN	CO ₂	S.G.	Volume	Cl mEq./L.		
11- 2-51	122.5	89.6	33.0	22.9	1.011	2.335	88.6	90/60	Weakness, cramps in legs, instability. Polyuria. Alb. 1+, WBC occ., RBC over 200.
11-13-51	125.0	92.3	55.3	19.9	1.001	1.555	40.2	116/60	Same. Nausea, slight edema of face and extremities.
11-21-51	125.5	—	—	—	1.009	2.690	88.1	—	Acute left failure.
11-29-51	129.3	97.5	—	22.8	1.006	4.380	113.2	160/70	Greatly improved. No longer cramps in legs.
12- 7-51	137.5	95.0	31.5	24.3	1.009	3.740	228.6	170/90	Dyspnea, 2+ edema of extremities. 1 c.c. Thimerin.
1- 7-52	—	—	—	—	1.013	3.050	198.1	136/80	Edema free. Ambulant. Alb. 0, WBC occ., RBC 10-15.

Laboratory Examination: The urine was mahogany colored, pH 5, and specific gravity varied from 1.002 to 1.012. Urinary proteinuria was 3 plus. Red cells in the urine were packed per high power field, and white blood cells and casts were 5 to 6 per high power field. Renal function studies revealed the following: Volhard's concentration test showed a specific gravity of 1.011; Addis count showed 412,740,000 red blood cells, 52,562,000 white blood cells and 640,000 casts. The phenolsulfonphthalein test showed a one hour total of 10 per cent excretion. The urea clearance (standard) revealed 11.25 per cent of normal. The hemoglobin was 42 per cent; the red blood count was 2,510,000; the white blood count was 18,850; and the sedimentation rate was 28/61. Serial blood cultures grew *Hemophilus influenzae*.

Blood chemistry values revealed the following: nonprotein nitrogen, 36.5 mg. per cent; serum bilirubin, 1.6 mg. per cent total, while the plasma albumin was 1.75 gm. and the albumin was 2.50 gm.

Course in the Hospital: The presence of subacute bacterial endocarditis in addition to evidences of frank heart failure gave rise to a very poor prognosis. The patient became mentally confused, and the blood pressure, which had been 140/70 mm.

* See table 4 and figure 3.

of Hg, dropped to 90/60 mm. of Hg. On October 28, after being placed on a strictly low sodium diet, he appeared to be worse. Blood chemistry determinations revealed a sodium of 122.5 mEq./L., the potassium 5.3 mEq./L., and the chlorides 89 mEq./L. CO_2 was 22 mEq./L. The patient's appetite was very poor, and while on a 1.5 gm. NaCl diet he consumed on the average only .5 to 1.0 gm. of sodium chloride. He was given supplementary sodium chloride orally and soon began to show some improvement. Despite the persistence of heart failure and the low serum sodium concentration, his urinary volume remained high, as did the excretion of sodium chloride, which exceeded the intake by 3 to 4 gm. A diagnosis of salt losing nephritis was made. The dietary intake of sodium chloride was increased to 5 gm. a day on November 28, and the urinary excretion was only slightly increased. However, the serum concentration of sodium very gradually rose. During this period the patient's weight and the degree of cardiac failure had remained constant. Following the introduction of this treatment his nonprotein nitrogen, which had risen to 55.3 mg. per cent, dropped to normal. Aureomycin and streptomycin were given for a period of six weeks, and he

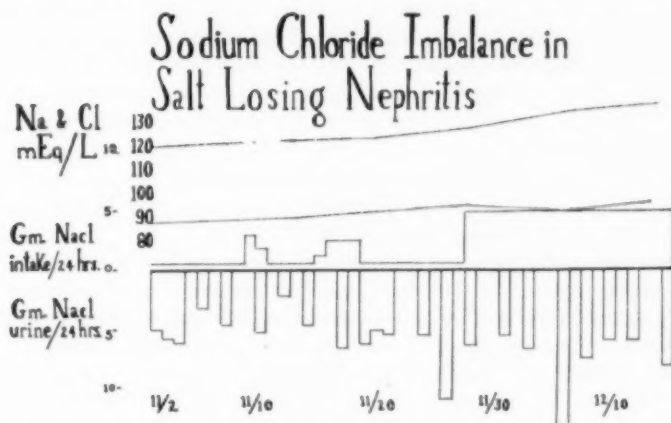


FIG. 3. Case 4. Note that, despite sodium chloride intake of about 1 gm. per day, excretion of sodium chloride continued on a high average level.

was given seven units of washed cell mass. The blood pressure rose gradually to normal. He cleared mentally and became strong and well enough to leave the hospital January 18, 1952.

It was believed that this patient had, in addition to subacute bacterial endocarditis, a focal embolic glomerulonephritis. It is believed also that he developed this salt losing syndrome during the acute glomerulonephritis, and that after the endocarditis and the embolic glomerulonephritis healed, the salt losing syndrome disappeared. Subsequent to his discharge on January 18, 1952, he has continued to make very satisfactory improvement.

COMMENTS

The most characteristic features of the salt losing disorder were exhibited in case 1. This patient had chronic renal disease which developed insidiously and was diagnosed chronic glomerulonephritis. He had the dehydration, the low blood pressure, no edema, a characteristic urinary picture

of polyuria with small quantities of albumin, a low specific gravity and no casts. The outstanding features were weakness and pain in the legs, mental confusion and vascular collapse, which disappeared along with other features of hypochloremia immediately following intravenous injections of salt solution and sodium lactate. Doses of DCA and cortisone were given without avail. The control of the salt losing syndrome has been maintained by the oral administration of 12 gm. of sodium chloride and 6 gm. of sodium bicarbonate daily. Within a period of weeks the blood urea nitrogen fell from a high level of 290 to 87 mg. per cent and remained at this lowered level during treatment. Although the chronic nephritis itself cannot be cured by such measures, the patient is quite comfortable and continues to be in a fair state of health.

Case 2 illustrates the difficulties of proper diagnosis of chronic renal disease. In this case, because of excessive intake of alkalis and the elevated carbon dioxide combining power of the plasma, a diagnosis of extrarenal uremia and alkalosis was made. It was not until later that the true nature of this disorder was recognized and the diagnosis of salt depletion syndrome was made. Doses of DCA were given without avail. The proper treatment was followed by a very satisfactory therapeutic response, and the patient has been controlled with supplementary sodium chloride tablets. A subsequent report reveals that for the past three years he has been progressing satisfactorily and is working at his occupation.

Case 3 illustrates chronic glomerulonephritis with hypertension. It soon became apparent that the patient maintained normal serum sodium concentration with difficulty. Urinary output of sodium chloride was independent of the level of serum sodium concentration, and despite decreased intake of sodium chloride the excretion remained fairly constant. Each time his serum sodium concentration fell he developed symptoms of weakness, vomiting and severe cramps of both legs. Edema was present on a cardiac basis. He did not develop hypotension during the low serum sodium concentrations; however, on entrance his blood pressure was high, and the level reached during the stage of sodium depletion may well be dependent upon the cardiovascular status of the patient before the onset of sodium depletion. Hence, the blood pressure recorded at this later time may truly represent a relative state of hypotension.

It is obvious that this patient had more complications than the salt losing syndrome, as he also had evidences of myocardial insufficiency and hypertension, as well as complications of chronic nephritis. Unfortunately, in the treatment of the salt losing syndrome the infusion of a 3 per cent sodium chloride solution was followed by acute pulmonary edema and death. It is very likely that the intravenous infusion was responsible to some extent for the sudden termination. At autopsy there was nothing specific in the tubules which could be held responsible for the remarkable clinical and chemical alterations seen.

Case 4 illustrates that the salt losing nephritis may develop during an acute renal disease and that the process in the tubular apparatus may be reversible. This patient entered the hospital with the classic story of valvular heart disease with congestive failure and the classic clinical picture commonly seen in these cases.

In addition, he developed subacute bacterial endocarditis and focal embolic glomerulonephritis. Following the initiation of a strictly low sodium diet for the edema he developed weakness, mental confusion and syncope. Determinations of the levels of sodium and chloride in the serum revealed hypochloremia and hyponatremia. On increased intake of sodium chloride he made rapid improvement. Mental confusion disappeared, and he became much stronger and felt well. A follow-up study revealed that there was a remission of the salt losing phase of this disease. At the present time he has no evidence of it and, with a minimal amount of treatment for his heart condition, is progressing satisfactorily. The salt losing tendency appeared to be a transient condition which has not been emphasized in other such cases.

DISCUSSION

The relationship of disturbed serum electrolyte pattern to renal insufficiency has been the subject of considerable investigation during the past years. Peters and his associates^{3,4} made extensive observations on total acid base equilibrium in health and disease with regard to the acidosis of nephritis and hypochloremia and total salt deficiency in nephritis. They point out that in uremia the sodium and chloride may be depleted, and that in treatment of advanced nephritis not only must administration of fluid be considered but attention must also be given the administration of salt to prevent salt depletion.

In uremia a tendency for deficiency in sodium and chloride may result from excessive loss in the urine in some of these cases. It has been pointed out by Peters and Van Slyke⁵ that the uremic patient appears to be able neither to concentrate salts in the urine when a high rate of excretion is desired nor to prevent their loss when conservation is urgently needed.

It is worth while to emphasize that the changes in the electrolyte pattern of the serum do not always correspond to the clinical picture. Many patients examined show the *chemical* evidences of a salt depletion in the blood serum but the *clinical* features of the salt depletion, as collapse, hypotension, muttering delirium, mental confusion, weakness, and painful extremities may not as yet have developed.

Thorn and his associates⁷ presented the study of two patients who on admission to the hospital were considered to be suffering from acute adrenal insufficiency. These patients were observed over a period of some two to four years, and postmortem examination proved that metabolic changes in the body followed renal rather than adrenal disease. Thorn states that the

most striking feature presented by the two patients was their ability to tolerate large quantities of sodium chloride, 10 to 15 gm. daily, and sodium bicarbonate, 4 to 6 gm. daily, without development of edema or hypertension in the presence of high grade renal insufficiency. This phenomenon persisted until one to two months prior to death. Although the salt losing tendency became quite modified toward the close, it apparently did not completely disappear. They emphasize that the interest in these cases is not only because of physiologic implications but also because of the correction of metabolic disturbances by proper therapy which led to rehabilitation of these patients for a number of years. As illustrated in the article, diagrammatically the adrenal hormone is adequate and the glands are normal, but for some unknown reason the tubules fail to respond to the normal stimulating influence of the adrenal cortical substance.

Significantly, at autopsy no specific lesion of the kidneys was found to account for the clinical picture described. Sawyer and Solez⁶ presented a case in which the first diagnosis made was Addison's disease, but the presence of severe tubular insufficiency and inability to reabsorb salt after the administration of DCA confirmed a diagnosis of chronic glomerulonephritis. The suprarenal glands were found to be normal. Their patient closely simulated the patients described by Thorn et al.⁷ Singularly enough, Sawyer and Solez' patient had chronic duodenal ulcer, as occurred in our second case.

Following these original reports, Nussbaum, Bernhard and Mattia⁹ reported the fourth case of this type described, a case of chronic pyelonephritis simulating Addison's disease. As they pointed out, there was no reason to suspect primary renal disease, as the urine was quite normal except for low specific gravity, no albuminuria and no casts. There were marked polyuria, azotemia, nausea and vomiting, and normal eyegrounds which led them to believe they were dealing with Addison's disease. Tests subsequently were performed to determine the degree of adrenal involvement, and a glucose tolerance test was normal, as was the Thorn test with ACTH, which revealed normal eosinophils. They too decided to observe the effects of cortisone on the kidney's electrolytes, and found that an elevation of the patient's morale was the only effect obtained. Complaints of weakness of the extremities and, at one time, paralysis of the lower extremities they attributed to a hyperkalemia and a hyponatremia. Their case illustrates how easily a disease as common as chronic pyelonephritis may be overlooked.

Bilateral cystic disease of the kidney may be the cause of chronic renal insufficiency and a salt depletion syndrome so severe that Addison's disease may be simulated. Borst¹⁰ reported a case suffering from chronic renal insufficiency and uremia caused by bilateral cystic disease of the kidney in whom significant changes were present in the metabolism of water and salt. As he pointed out, the kidneys continued to excrete salt even though the concentrations of sodium and chloride in the plasma were far below the normal value. A status similar to that seen in Addison's disease and certain infec-

tions developed. In Borst's case the blood urea concentration, which had been 583 mg. per cent on the first day and had risen by the following day to 600 mg. per cent, fell rapidly with the treatment of sodium and chloride given intravenously. If intravenous transfusions of fluid were stopped for several days, dehydration and a rapid rise in blood urea followed quickly. In Borst's case, miliary tuberculosis led to the patient's death, and at autopsy no abnormalities were found in the suprarenal glands.

Joiner and Thorne¹¹ reported three cases of salt losing nephritis, with the description of the clinical picture and the findings at autopsy. The clinical features closely paralleled those described by other authors and those of our own cases. In these three cases the diagnosis lay between Addison's disease and chronic nephritis. The final diagnosis in all three cases, however, was chronic pyelonephritis.

The pathologic changes in the kidneys in salt losing nephritis are the subject of an article by Enticknap.¹² The author discusses the pathologic and histologic changes in the kidney of all of the cases so far reported. It is his opinion that chronic pyelonephritis was the proper diagnosis in four of them, that it was probably present in six of them, and may well have been present in all eight cases. In his discussion he points out that the terms "chronic glomerulonephritis" and "chronic pyelonephritis" must be more carefully defined. He suggested that chronic pyelonephritis is the condition commonly responsible for the salt losing syndrome, and he says: "As used here it is almost synonymous with the chronic interstitial nephritis of the older descriptions, a term which might well be applied to all the kidneys referred to. Its main feature is the presence of a chronic inflammatory exudate in the interstitial tissue causing renal contraction that is commonly greater on one side than the other. Microscopically a reticular type of fibrosis is seen, and the most typical lesion is a radial band extending from the pelvic region to a coarse depressed stellate scar on the surface. Parenchymal lesions are mainly confined to these bands of scar tissue, in which tubular atrophy and glomerular hyalinization together with arteriolar sclerosis and hyalinization are commonly found. In between these scars tubular hypertrophy and dilatation are present, and in many cases this proceeds to the stage of formation of small cysts in which the so-called colloid casts may be seen." In Dr. Enticknap's appraisal, the histologic material submitted so far would fit better into a diagnosis of chronic pyelonephritis than any other type of Bright's disease. He suggests that the term "salt losing nephritis" is not an accurate one, and that perhaps some other term might well be applied.

The urinalyses in nearly all the cases so far described disclose either minimal quantities of albumin in the urine or, in some cases reported, none at all. A low specific gravity was also a common feature. The urinary picture is held by Enticknap¹² to be not one of chronic nephritis but, in most instances, one of pyelonephritis.

In reviewing the literature, chronic glomerulonephritis was the histologic diagnosis in three cases, polycystic kidney in one, pyelonephritis in three, and tuberculosis and pyelonephritis in one. In our report of four cases, cases 1, 2 and 3 were considered chronic glomerulonephritis. Histologic examination in case 3 confirmed the clinical diagnosis of nephritis. In case 2, although the diagnosis of chronic glomerulonephritis was made, in retrospect it is possible that it was a case of chronic pyelonephritis. Case 4 was definitely proved to be an acute or subacute embolic glomerulonephritis from subacute bacterial endocarditis.

In spite of the different kinds of renal disease reported, it is observed that one feature is common to all—disturbance of the tubular system. Although there does not appear to be a specific histologic change, there is a common physiologic difficulty, namely, the failure to conserve sodium and chloride in a normal way. As this failure has been considered in some of the cases to be associated with other manifestations of Addison's disease, the differentiation from Addison's disease has been a problem to be solved. The failure of the tubular epithelium to respond to DCA and cortisone and ACTH, as would be expected in a case of Addison's disease, is well illustrated diagrammatically by Thorn et al.,⁷ who show that the tubular epithelium is incapable of responding to the stimulation of the adrenal hormone, and that the disorder is one intrinsic in the tubular cells rather than in the endocrine system.

All of the patients so far reported show a rather fixed pattern as far as the clinical features are concerned. They follow very closely the one emphasized by Thorn et al.⁷ in their original report. Chronic renal insufficiency develops insidiously into uremia and, because of certain characteristics, these patients may so closely simulate Addison's disease that confusion in diagnosis results. In our cases, the question of Addison's disease arose for consideration in two cases. Although the diagnosis was not clear at first in the other cases, Addison's disease was not considered. Almost any kind of chronic renal disease, as it progresses towards termination, may end with this clinical syndrome. It is to be observed, however, that the chronic renal disease is usually progressive in spite of the adequate treatment of the salt losing syndrome.

Landis et al.⁸ showed that, under the influence of a limited salt intake in patients suffering from nephrosclerosis or chronic nephritis, urea clearances fell while nonprotein nitrogen rose. Then, if sufficiently large amounts of saline were given intravenously, urea clearances rose and the blood non-protein nitrogen fell. They made observations on the sodium chloride restriction and the urea clearance in renal insufficiency, and reported a patient with chronic glomerulonephritis who showed vomiting, convulsions, oliguria, a blood urea of 542 mg. per cent, and a blood chloride of 250 mg. per cent. The administration of sodium chloride intravenously diminished the oliguria and eventually lowered the blood urea to 25 mg. per cent. They state that

the identification of the exact mechanism by which renal function can be reduced during chloride restriction must await further opportunity to study other patients with hypochloremia and azotemia.

It seems wise to suspect this salt losing syndrome in all cases of chronic renal insufficiency with impending uremia. The recognition of this abnormality, followed by adequate treatment, leads to satisfactory therapeutic responses and years of comfort added to the life of the patient. Obviously, the basic primary renal disturbance is responsible for the course and prognosis. At the present time, however, when restriction of salt has become so popular in the treatment of nephritis, edema, heart disease and hypertension, it is desirable to be especially alert for this salt losing syndrome. This is especially so if salt removing resins are employed in treatment, as they so commonly are. It would not be surprising to find many more cases of salt depletion syndrome if these measures continue to be as popular as they have been. As pointed out by Black and Litchfield,¹² when low salt diets are used the blood urea should be estimated frequently. As it rises materially, a low sodium diet should be replaced with one containing a normal amount of sodium. And if uremia seems to be impending, injections of intravenous saline solutions should be resorted to. The promiscuous use of salt restrictions, sodium removing resins and mercurial diuretics is to be avoided, especially when renal insufficiency is imminent. Patients should be individualized, and a careful evaluation of the electrolyte constituents of the serum determined.

In most cases of chronic renal insufficiency the terminal phase usually diagnosed uremia may be greatly modified by the correction of the abnormalities of the electrolyte pattern.

SUMMARY

1. Four cases of renal disease exhibiting so-called "salt losing nephritis" are added to the eight already published in the literature.
2. Many patients show the chemical evidences of a salt depletion in the blood serum, but the clinical features of the salt depletion, such as collapse, hypotension, muttering delirium, mental confusion, weakness and painful extremities, may not as yet have developed. At autopsy no specific lesion of the kidneys is found, although in the histologic material of all cases submitted so far it would appear that chronic pyelonephritis is most common. This was not the case in our experience, as three cases had chronic glomerulonephritis and one was an acute or subacute embolic glomerulonephritis from subacute bacterial endocarditis.
3. One physiologic feature common to all the cases reported is the disturbance of the tubular system, namely, the failure to conserve sodium and chloride in a normal way. As this failure has been considered in some cases to be associated with the manifestations of Addison's disease, the differentiation from Addison's disease has been a diagnostic problem.

4. It seems wise to suspect this salt losing syndrome in all cases of chronic renal insufficiency with impending uremia, and to be aware of the condition in these days when restriction of salt has become so popular in the treatment of nephritis, edema, heart disease and hypertension. The recognition of this abnormality, followed by adequate treatment, may lead to gratifying therapeutic responses and years of comfort added to the life of the patient.

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LOCALIZED INTERLOBAR EFFUSION IN CONGESTIVE HEART FAILURE*

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LOCALIZED interlobar effusion due to congestive heart failure ("vanishing tumor" of the lung) is thought to be rare. Gefter, Boucot and Marshall¹ recently reviewed the literature and added four cases. The purpose of this paper is to estimate the prevalence of "vanishing tumor" in order to evaluate its importance in the differential diagnosis of chest lesions, and to discuss the recognition of this entity. Data available at the photofluorographic unit of the Philadelphia General Hospital were used as a basis for study. Such a survey instrument provides a method for uncovering more examples of this interesting entity.

During the calendar year 1951, 33,084 photofluorograms were taken at the Philadelphia General Hospital survey unit. The individuals surveyed were composed largely of hospital admissions, receiving ward and dispensary patients, and smaller groups of employees, hospital visitors, etc. The miniature 70 mm. films were routinely read by the same certified roentgenologist. All those read as revealing significant abnormalities were reviewed by a chest specialist (W. W.). Criteria for survey suspicion of "vanishing tumor" were an enlarged heart or abnormal cardiac silhouette and a density in the region of one or more of the interlobar fissures, especially on the right side. The diagnosis of localized interlobar effusion due to congestive heart failure was confirmed by demonstrating the disappearance of the lesion as congestive heart failure improved with therapy.

ANALYSIS OF CASES

Five proved cases of "vanishing tumor" were found through routine reading. The ages of the patients (table 1) ranged from 46 to 76 years. All but one were males. Four had underlying hypertensive or arteriosclerotic heart disease, and one was rheumatic. The interlobar effusions were all on the right side: three in the transverse fissure and two in the oblique fissure. The majority of reported cases had effusions in the transverse fissure. In one case (L. F.) there was some free fluid at the base of the right pleural cavity as well as in one interlobar space. A previous history of pleurisy was obtained in only one patient.

It is interesting that the roentgenologist assigned to the photofluoro-

* Received for publication January 21, 1953.

From the Philadelphia General Hospital and the Woman's Medical College of Pennsylvania.

TABLE I
Analysis of Cases

Name	Age	Race	Sex	Clinical Cardiac Diagnosis	Location of "Tumor"		Initial Survey Readings
					Rt. Transv. Fissure	Rt. Oblique Fissure	
F. F.	76	W	M	Arteriosclerotic	X		Neoplasm or lung abscess
W. J.	46	C	M	Hypertensive	X		Tuberculosis or neoplasm
L. F.	47	C	M	Hypertensive		X	Tuberculosis or pneumonia
A. W.	56	W	F	Rheumatic	X		Tuberculosis or bronchiectasis
G. S.	62	W	M	Arteriosclerotic		X	Neoplasm or pneumonia

graphic unit failed to suspect the true nature of the pulmonary abnormality in every case in spite of his familiarity with this condition. Initial survey readings (table 1) included neoplasm, tuberculosis, pneumonia, lung abscess and bronchiectasis. The frequent impression of tuberculosis is the result of a deliberate policy of "over-reading" survey films for tuberculosis.

Two of the five patients died and were autopsied. The postmortem findings support the thesis that "vanishing tumor" of the lung occurs in patients with congestive heart failure and obliterative pleuritis.



FIG. 1A. Posterior-anterior roentgenogram of patient F. F., May 24, 1951, showing interlobar effusion in the transverse fissure.

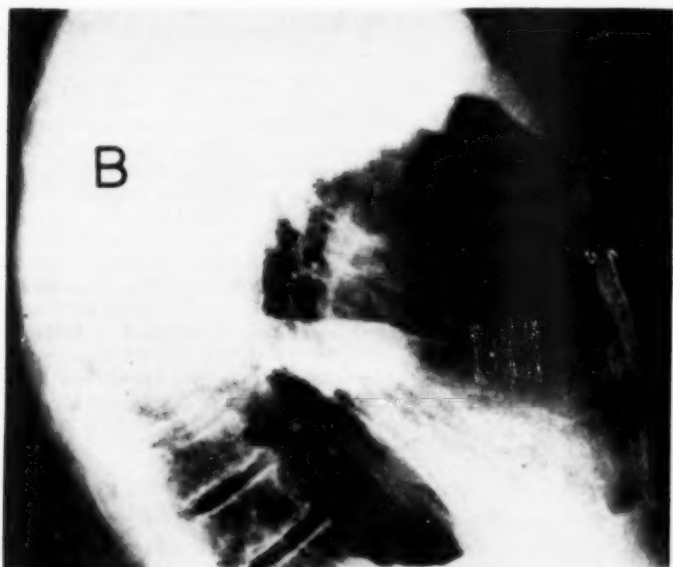


FIG. 1B. Lateral roentgenogram of patient F. F., May 24, 1951, showing interlobar effusion in the transverse fissure.

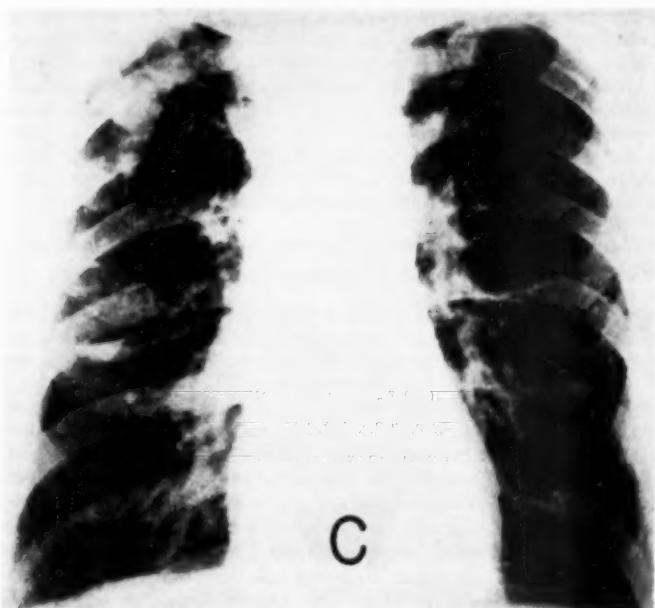


FIG. 1C. Roentgenogram of patient F. F., June 13, 1951, showing almost complete absorption of the interlobar fluid.

CASE REPORTS

Case 1. The first patient (F. F.) was a 76 year old white male with arteriosclerotic heart disease, congestive heart failure and auricular fibrillation. A chest film taken on his admission to a medical ward showed an irregular circumscribed density in the right midlung field, with obliteration of the right costophrenic sulcus (figure 1A). Because a pulmonary neoplasm was suspected, the patient was bronchoscoped and the findings were normal. A lateral chest film (figure 1B) revealed the lesion in the transverse fissure; there was also thickening of the oblique fissure. A film (figure 1C) taken after three weeks of digitalis therapy and bed-rest showed almost complete disappearance of the density. The patient was found to be anemic, and studies later revealed that he had chronic myelogenous leukemia. Meanwhile he again developed evidence of congestive failure, and the interlobar effusion reappeared three months after admission. Ammonium chloride and Thiomerin were added to his therapy, and the frequency of mercurial injections was gradually increased, without effect on his failure. The patient died four and a half months after admission. Autopsy revealed chronic myelogenous leukemia, organizing pneumonia in all lobes, pulmonary congestion and edema, complete fibrous obliteration of both pleural cavities, effusion in the transverse fissure, cardiac dilatation, and acute and chronic pericarditis with leukemic infiltration of the serosa of the heart.

These findings are of interest for two reasons: first, the interlobar effusion was demonstrated post mortem; second, there was complete obliteration of the rest of the pleural cavity. Failure of the patient's cardiac decompensation to respond the second time to adequate therapy was probably influenced by the leukemic infiltration of the cardiac serosa and the pericarditis.

Case 2. The second autopsied patient was W. J. (figure 3), a 46 year old Negro male admitted to the medical ward with hypertensive cardiovascular disease and congestive heart failure. He was treated with rest, salt restriction and digitoxin. Thiomerin was given infrequently during the first two weeks of hospitalization. The interlobar effusion persisted. Mercurials were administered on five successive days and the interlobar effusion then disappeared. The patient failed to improve and died one month after admission. Autopsy revealed malignant nephrosclerosis and fibrous obliteration of the right pleural cavity. An unobliterated space was found in the right transverse fissure but it did not contain fluid.

The above case and the remaining three cases illustrate how the rapidity with which the interlobar fluid disappears varies with the vigor of therapy.

Case 3. L. F., a 47 year old Negro male, was admitted to the hospital with hypertensive cardiovascular disease, congestive failure, thrombosis of the left femoral artery and gangrene of the toes. A photofluorogram on admission showed the presence of free fluid at the right costophrenic sulcus, a hazy density in the right lower lung field and an enlarged heart. Therapy consisted of rest, digitalis, salt restriction, ammonium chloride and Thiomerin injections. Figure 2 illustrates the slow disappearance of the interlobar effusion, with gradual decrease in cardiac size over almost three months. Mercurials were given daily only during the first five days of hospitalization. Thereafter they were given sporadically, and the interlobar fluid was absorbed slowly. The patient was transferred to a surgical ward for amputation of his left leg about four weeks after admission. At this time mercurials were discontinued, although the interlobar fluid had not completely disappeared. Another photofluorogram was taken seven weeks later and the interlobar collection was gone.

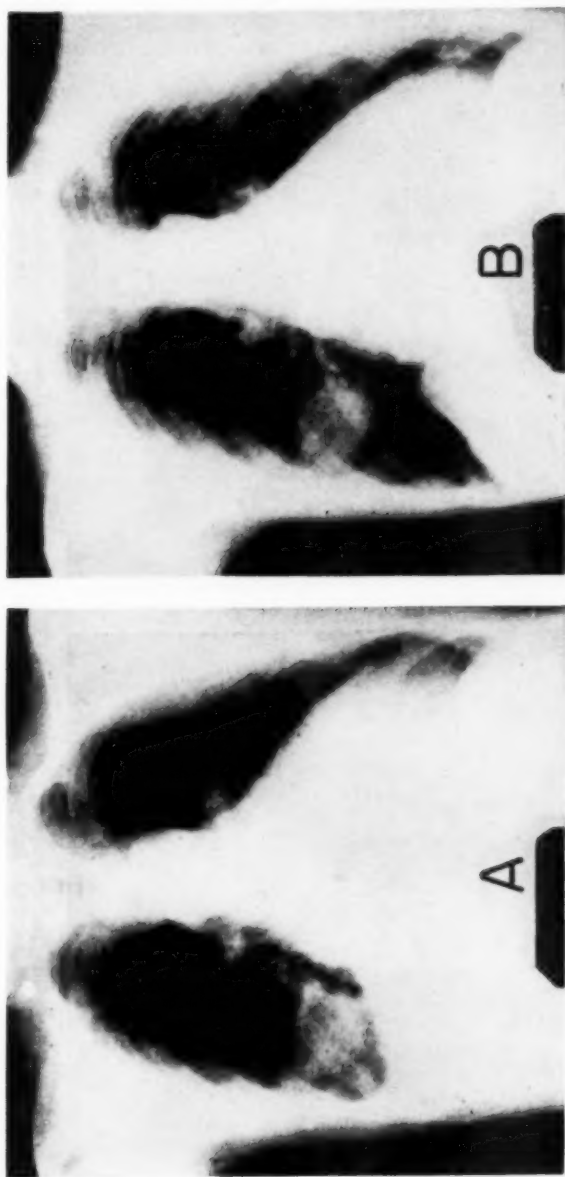


FIG. 2. Chest films (photofluorograms) of patient L. F. A, October 2, 1951, shows condition on admission to a medical ward, with a vague round density at the right base and a small amount of free pleural fluid. B, October 8, 1951, shows disappearance of the free pleural fluid; the interlobar collection in the oblique fissure is more discrete.

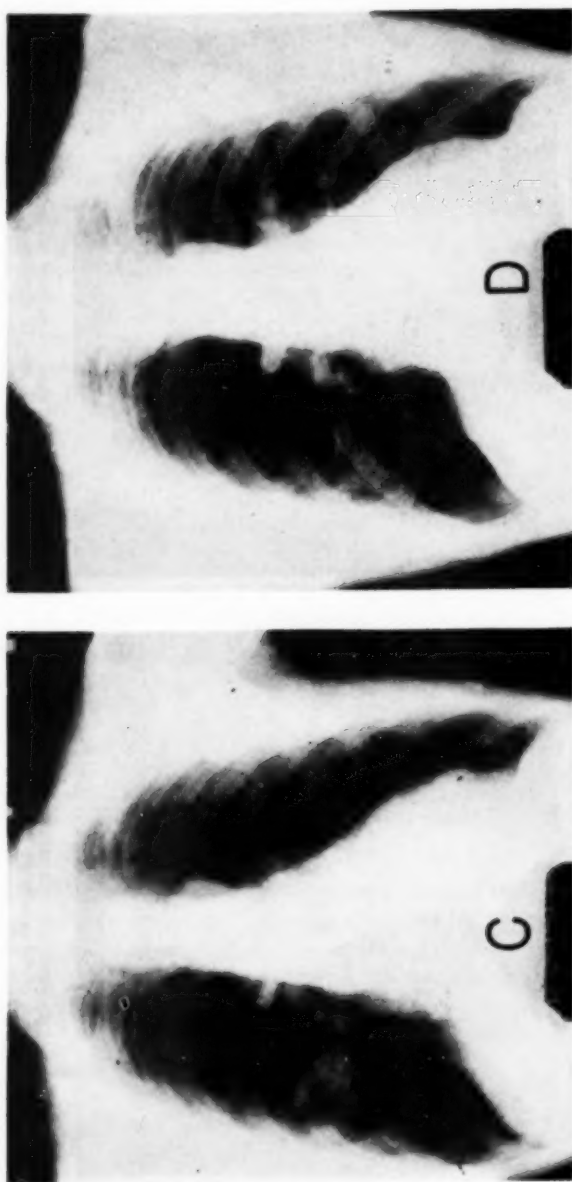


FIG. 2. Chest films (photofluorograms) of patient L. F. C. October 22, 1951, shows the heart to be considerably smaller, while the shadow of the interlobar fluid is less dense and smaller. D, December 24, 1951, shows complete disappearance of the "vanishing tumor."

It is probable that the enforced inactivity occasioned by the amputation was an important factor in the final absorption of the interlobar fluid.

Case 4. G. S., a 62 year old white male, was admitted to a medical ward with arteriosclerotic heart disease, cardiac decompensation and diabetes mellitus. His interlobar collection (figure 3) responded within four weeks to rest, digitalis, salt restriction, ammonium chloride and frequent mercurial injections. One year later he returned for a repeat film, which showed reappearance of his interlobar effusion.



FIG. 3. Diagrammatic representations of photofluorograms in three cases.

Hospitalization was recommended and three weeks later he was re-admitted to a medical ward. A photofluorogram on admission, to our surprise, revealed no "vanishing tumor." On questioning, he disclosed that he was in the habit of giving himself the mercurial injections once or twice a week. At the time we obtained a film showing the interlobar collection, he began to feel dyspneic and increased his frequency of self-administration to every second day. The resulting diuresis accounts for the disappearance of the interlobar fluid.

Case 5. A. W., a 56 year old white female, was admitted to a medical ward

with rheumatic heart disease and congestive failure. A photofluorogram done three days prior to admission showed an enlarged heart, pulmonary congestion, and a small round mass in the peripheral right midlung field (figure 3). The patient was treated with ammonium chloride and three daily intramuscular injections of a mercurial. Four days after admission the patient was discharged against advice. A second photofluorogram at this time showed disappearance of both the pulmonary congestion and the round mass.

PREVALENCE OF "VANISHING TUMOR"

The prevalence of "vanishing tumor" was five cases among 33,084 individuals x-rayed. Of those surveyed, 7,577 were hospital admissions. The field can be further narrowed to surveyed medical ward admissions, a group numbering 2,234 (representing only 54 per cent of medical admissions during this period). Among these medical admissions, "vanishing tumor" had a prevalence of 0.22 per cent.

It is apparent that the "vanishing tumors" were discovered among those individuals ill enough to require hospital admission. This is in keeping with the fact that among 96,554 Philadelphia food handlers x-rayed since January 1, 1949, not one "vanishing tumor" has been found despite the fact that one of us (K.R.B.) has been on the alert for this possibility. Apparently it occurs only in cardiac failure of sufficient degree to allow the accumulation of pleural fluid.

These figures suggest that "vanishing tumor" is as uncommon a condition as the literature indicates.

THE RECOGNITION OF "VANISHING TUMOR"

An attempt was made to measure the index of suspicion for "vanishing tumors." A roll of 466 photofluorograms from the year 1951 was pulled from the file without any knowledge of its content. All films originally read as revealing significant abnormalities of any kind had been cut from the roll and filed with the patients' records. These abnormal photofluorograms, including those of the five cases with "vanishing tumor" were inserted haphazardly into the roll by a stenographer. Two certified radiologists and two certified internists particularly interested in chest diseases were asked to read this roll of film. None of these individuals was aware of the nature of this study but all were known to be familiar with the entity of "vanishing tumor." Each reader was asked to review the roll and give his diagnostic impressions regarding every abnormal photofluorogram. No other information was given to the readers. The number of abnormal films read by these individuals varied from 44 to 88. Such variation is usual.² The diagnostic impressions of each reader for each of the five cases of "vanishing tumor" are given in table 2. It will be noted that each radiologist recognized the "vanishing tumor" in three of the five cases, but one internist found only one and the other internist failed to recognize any. One case was

TABLE II
Recognition of "Vanishing Tumor" of the Lung

Patient	Radiologist No. 1	Radiologist No. 2	Internist No. 1	Internist No. 2	No. of Readers Recognizing Each "Vanishing Tumor"
F. F.	Localized interlobar effusion	Localized interlobar effusion	Pulmonary fibrosis and thickened pleura	Tuberculosis	2
W. J.	Localized fluid or infarction	Interlobar effusion	Pneumonic patches	Tuberculosis or Hodgkin's disease	2
L. F.	Interlobar effusion or malignancy	Interlobar effusion	Lung tumor or interlobar effusion	Primary carcinoma	3
A. W.	Pneumonia and bronchiectasis	Bronchiectasis	Pulmonary fibrosis and bronchiectasis	Tuberculosis and bronchiectasis	0
G. S.	Neoplasm	Pneumonia or infarction	Pneumonia	Tuberculosis	0
No. Recognized by Each Reader	3	3	1	0	

recognized by three readers, two cases by two readers, and two cases were not recognized by any reader.

It is apparent from this experiment that "vanishing tumors" are not often recognized.

DISCUSSION

Since the report of Gefter, Boucot and Marshall,¹ two additional reports^{3,4} have described single cases of localized interlobar effusion in congestive heart failure. Feldman² reiterated the theory of Stein and Schwedel⁵ that a congenital indentation in the region of the interlobar fissure explained the localization of the fluid. He used this as an explanation in those cases which also show free fluid at the base of the pleural cavity. However, it seems unnecessary to invoke such a theory to explain "vanishing tumors," because an obliterative pleuritis need not affect the entire pleural cavity. It is probable that the localization of obliterative pleuritis in such cases spares both an interlobar fissure and the base of the pleural cavity but seals off the interlobar fissure from the rest of the pleural cavity. Thus fluid may collect in both places. As a matter of fact, all of the few autopsied cases, including our own, have failed to reveal a congenital indentation of the interlobar fissure, but all cases have shown obliterative pleuritis of part or all of the pleural cavity.

Since localized interlobar effusion may simulate tumor, it is important to make a distinction. Peripheral bronchogenic carcinoma may occur in a patient with congestive failure. "Vanishing tumor" may also be confused with pleural fibroma of the interlobar fissure⁶ if the latter occurs in a patient with congestive heart failure.

The diagnosis of "vanishing tumor" is important for therapy. Lateral chest films will facilitate prompt recognition. The roentgenographic appearance of localized collections of fluid deserves emphasis. The lateral chest film helps to determine whether a collection of fluid is in the plane of a

fissure. When the fluid is in the oblique fissure, it tends to be hazier and less well demarcated than a collection in the transverse fissure on the posterior-anterior roentgenogram. In the oblique fissure the fluid is spread out in a plane which is not parallel to the direction of the x-rays as they pass through the chest. Therefore, the x-rays pass through less fluid than in the case of a collection in the transverse fissure, and the shadow cast is less dense. Associated evidence which points to "vanishing tumor" in the roentgenogram consists of cardiac enlargement with pulmonary congestion.

The response to therapy varies considerably, depending primarily on the vigor with which therapy is pursued. Clinical evidence of congestive failure generally disappears prior to the disappearance of the interlobar effusion. Since the effusions are buried in the fissures, physical signs of their presence cannot be detected. In some cases we demonstrated with frequent photofluorograms that a "vanishing tumor" may be a subclinical manifestation of congestive failure.

SUMMARY

1. Five cases are reported of "vanishing tumor" of the lung found within a period of one year among 33,084 photofluorograms taken at a large general hospital.
2. Evidence is presented that the lesion is relatively rare. Among 2,234 photofluorograms taken on admissions to the medical wards, the prevalence was 0.22 per cent.
3. The theory that obliterative pleuritis is essential to the formation of a localized interlobar effusion due to congestive heart failure was supported by the autopsy findings in two cases.
4. The lesion may not be recognized and errors in management may occur.
5. The response to cardiac therapy varied with the vigor of treatment.
6. The presence of a "vanishing tumor" may be a subclinical sign of congestive failure.

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ON THE ISCHEMIC BASIS OF "PEPTIC" ULCER. I. HISTORICAL DEFINITION OF PRESENT STATUS*

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THE NECESSITY FOR ASSUMING AN ISCHEMIC BASIS FOR THE ULCER PROCESS

It no longer appears necessary to initiate a discussion of peptic ulcer with a candid statement to the effect that nothing is known of its etiology. During the past few years a changing attitude toward ulcer genesis has been reflected in an increasing impatience with emphasis on gastric secretory activity, and with the many thousands of hours which have been spent on the study of secretory responses under various physiologic and pathologic conditions. Although resistance against assumed importance of the acid-peptic factor was expressed as early as the fifth decade of the Nineteenth Century—largely in Central Europe and largely as a reaction to Beaumont's¹ work—the literature of the 1850–1950 period has been singularly weighted on the side of secretory investigation. Few objections were raised to the acid-peptic factor as the cause of ulcer. The objection that the gastrointestinal tract appears to be immune to autodigestion was attacked from several directions. The most popular, perhaps, has been the theory that gastritis first depresses mucosal vitality, producing the necessary locus minoris resistentiae for ulceration. The tremendously interesting contributions of Konjetzny² in this connection are well known; however, they, as well as those of other students of gastritis, have proved insufficient to carry the argument.

The keystone for a proper theory of ulcer genesis will be found in identification of the mechanism responsible for local depression of mucosal resistance. When there is spontaneous loss of substance from any other surface of the body, to form an ulceration, the basic cause of tissue dissolution is ischemia, whether the initiating process be infection, trauma, thermal influence or neoplastic change. Both clinical observation and experimental study have rendered it inconceivable that native gastric acid, however concentrated, could produce an ulcer under conditions of normal mucosal health. Furthermore, because acute ulcers may heal spontaneously, without acid neutralization, under both experimental and normal conditions, and because there is no close correlation between specific acid levels and ulcer incidences, the explanatory mechanism would have to include the features of rapid influence over mucosal viability and at least a degree of independence of secretory activity. Other less direct circumstances, such as the influence of

* Received for publication November 26, 1952.

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sudden temperature changes on relapses, the part played by stress situations, and the general vasomotor hyperirritability of the ulcer patient, make it necessary to assume that the causal mechanism is capable of coming under the control of certain systemic and environmental factors. When considered on this rather superficial plane, local vascular insufficiency appears to be the first factor to require consideration.

Theories of peptic ulcer genesis based on mucosal ischemia have been proposed time after time, but such theories (if not the thought behind them) have regularly been short-lived because there was no anatomic information to permit explanation of localized mucosal ischemia. It has long been known that the blood volume of the total mucosa varies quickly under many physiologic and abnormal conditions. The general response, manifesting itself by alternating mucosal engorgement and blanching, has been considered to depend on such general reactions as contractile changes in the mucosal arteries³⁻⁷ and the influence of muscularis mucosae contractions on the penetrating vessels. But ulcer genesis could not be explained by such a general mechanism because ulcers usually occur singly and they regularly represent sharply circumscribed lesions. Necessity for briefness does not permit proper presentation of the great amount of important work that has been accomplished on these matters. One should study thoroughly the experimental details and arguments as outlined by Hauser⁸ and by Ivy, Grossman and Bachrach.⁹

Long before emphasis was concentrated on acid-peptic matters—in fact, just 100 years ago—both Virchow¹⁰ and Rokitansky¹¹ saw clearly that ischemia must be the basis for “peptic” ulcer. Without a doubt in his mind, Virchow postulated that ulcer is due to organic or spastic closure of a mucosal artery, followed by anemic necrosis and autodigestion. But even the medical statures of Virchow and of Rokitansky failed to keep the postulate active, because neither the occlusive mechanism nor the mechanism for localization selectivity could be explained by extant knowledge of normal submacroscopic anatomy.

THE NECESSITY FOR ASSUMING CEPHALIC INITIATION AND SECRETORY COMPLETION OF THE ULCER PROCESS

There can be little question but that the concept of psychosomatism, in its more general implication, exerts its behind-the-scenes control over selection of candidates for the ulcer process. Any theory which did not recognize this influence—whatever the use made of it—could hardly be acceptable. Similarly, there are enough clinical and experimental data implicating faulty adaptation to stress situations, as the initiating force in the psychosomatically ripe ulcer prospect, to necessitate inclusion of the concept of the General Adaptation Syndrome.

But the real etiologic problem of today revolves about mediation of the primary ulcerogenic influences, rather than the nature of those primary in-

fluences themselves. It can be agreed that the acid-peptic factor is responsible for the mechanical work of ulceration, once mucosal resistance has been affected. Both the cephalic and acid-peptic factors are believed to be essential in the process, but it is important to understand how their rôles are limited: they are responsible only for initiation and completion. To maintain perspective they are mentioned under a separate heading here.

LOCAL AND GENERAL ARTERIAL DISEASE

First, it is helpful to consider the problem of arterial disease in the ulcer patient. One should study Spang's¹² monograph of 1948 on the matter.

Müller and Heimberger¹³ observed that among ulcer patients the capillaries of skin, lips and gastric mucosa show abnormal tortuous changes. This finding, confirmed in part by Berti-Riboli and Verneti,¹⁴ has proved confusing because it has engendered assumption of functional abnormality. No primary dynamic incompetence at the capillary level is known in the stomach or duodenum of the ulcer patient.

For the most part, abnormality of the larger artery, with anatomic evidence of actual circulatory deficiency, has been emphasized.¹⁵⁻²² There is an extensive literature supporting the thesis that the ulcer patient is more likely to have generalized vascular disease than the ulcer-free population.²³⁻³¹ In general the data and arguments are not convincing. The observed incidences of generalized arterial disease have been for the most part on the order of Moore's²¹ figures of 1883: 28 instances of vascular degeneration among 114 cases of gastric ulcer. Woolf's³² injection studies demonstrated saccular and fusiform dilatations, striking variation in tortuosity, angulation, and arterial constrictions in the branches of the gastric arteries of persons with ulcer, but there were too few cases to permit conclusions. One may note in passing that the less common widespread arterial diseases, such as Buerger's disease,³³ have from time to time been reported in association—usually coincidentally—with ulcer.

As interesting as they may be from the static pathologic point of view, investigations into intramural vascular conditions in the immediate vicinity of ulcers³⁴⁻³⁹ have not furthered etiologic understandings. Most vascular disease found here must be assumed to be secondary. It was the important observation of Key,⁴⁰ following careful injection studies, that there is widespread vascular occlusion in the base of and in the submucosa adjacent to chronic ulcers; however, no such occlusion could be found in the neighborhood of acute ulcers—indeed, acute hypervascularity was found in the submucosa in such cases. The work of Betz⁴¹ on arteriolar intimal fibrinoid necrosis associated with ulcer was especially important and permits the conclusion that local arterial obstructive disease is a consequence of secondary local circulatory disturbance rather than of primary vascular inflammatory change. To forestall anticipated objection to the present authors' full acceptance of Betz's conclusions, it should be pointed out that under certain

unusual clinical circumstances erosions and ulcers must, of course, be secondary to local primary inflammatory vascular disease. Thus, the mucosal disease of uremia, the toxemias of pregnancy, and chronic exogenous poisonings is primarily a vascular one and often leads to ulceration.⁴²⁻⁴⁵

De Busscher⁴⁶ observed that local endophlebitis may at times be found in the neighborhood of an ulcer.

INFLUENCE OF CERTAIN ANATOMIC AND PHYSIOLOGIC PECULIARITIES

Simple anatomic peculiarities of the gastroduodenal vasculature have been cited as potentially ulcerogenic, especially as they might explain favored ulcer sites, and this facet of the problem constitutes a long historical story. Much can be immediately discarded because it is based on the erroneous assumption⁴⁷ that arterial branches which reach the gastroduodenal wall are end-arteries. Reeves,⁴⁸ whose work was outstanding, found an anatomic explanation other than end-arteries for local mucosal ischemia and preferential ulcer sites. He observed that circulation in the submucosal arterial plexus tends to be slower along the lesser gastric curvature and in the duodenal bulb than in other parts of the stomach, because arterial diameter is smaller, vessels are longer, and arteriolo-arteriolar anastomoses are fewer. Observation that injection into any one of the arteries to the stomach could fill the entire plexus and, indeed, the greater part of the superior mesenteric distribution should effectively dispose of the question of end-arteries. Those arteries along the lesser curvature which do not enter into the submucosal plexus directly achieve communication with the remainder of the vasculature in the rich arborization within the mucosa.

Cole's⁴⁹ effort to implicate penetrating angles and tensions upon the extragastric branches of the left gastric artery was interesting but, in retrospect, futile.

In the course of extensive studies on the gastric vasculature, De Busscher⁵⁰ confirmed a previously proposed theory that the muscularis mucosae can influence the distribution of blood in the mucosa. He demonstrated by injection technics that partition of the blood mass was uniform through the mucosa if injections were made when the muscularis mucosae was at rest. Multiple areas of relative anemia were found below the neck zone of the mucosa when only portions of the muscularis mucosae were contracted, although such contraction never shut off the arterial supply entirely. He explained the effect in part by the angle of traversion assumed by the smaller mucosal arteries in their courses through the muscle layer. In the stomach, he pointed out, the muscularis mucosae is heaviest along the lesser curvature, the region preferred by gastric ulcers. It was concluded that by its contraction the muscularis mucosae might be responsible under natural conditions for temporarily ischemic zones in the mucosa, and thereby could be indirectly responsible for tissue breakdown and ulceration.

MAJOR OCCLUSION OF THE GASTRIC ARTERIES

As common as tiny emboli to the gastric mucosa may be (*vide infra*), major vascular accidents involving portions of the whole gastric wall are very rare. The arterial system of the stomach is so arranged anatomically that any arterial occlusive process must be most extensive before the degree of mural ischemia can become significant, but, paradoxically, acute ulcers may quickly follow minute emboli to the mucosa. Even though all but one gastric artery be ligated, the submucosal arterial plexus, which surrounds the organ, is rich enough that all parts receive satisfactory circulation.

The effects of partial devascularization have been studied in some detail.⁵¹⁻⁵⁵ It has been found in dogs that ligation of two or three of the four large gastric arteries has no significant effect on gastric secretory activities. Neither does it have any significant effect on gastroscopic appearances. No amount of arterial ligation short of total devascularization will lead to erosions, hemorrhages or ulcerations.⁵⁹⁻⁶¹ Only inconsequential alteration of mucosal histology follows 90 per cent devascularization.⁶² Occlusion of all four of the large arteries supplying the canine stomach, on the other hand, results in total gastric infarction.

Baronofsky⁶³ evaluated the ability of experimental artery ligation to prevent ulceration induced by the histamine-in-beeswax technic. Surgical procedures effective in preventing histamine-in-beeswax ulcers in dogs have proved reliable in the clinical treatment of duodenal ulcer. It was found that ligation of the left gastric and both gastroepiploic arteries, plus five of every six branches of the gastroepiploics, afforded no protection against ulcer.

It was largely Somervell⁶⁴—the same Somervell who climbed to a higher altitude on Mount Everest without oxygen than has any other man—who was responsible for clinical popularization of artery ligation for treatment of duodenal ulcer. His report was enthusiastic. Wood⁶⁵ employed Somervell's technic in 47 patients, and, although his first impression was one of reasonable satisfaction, an evaluation from one and one-half to four years postoperatively changed his opinion, largely because he found three instances of jejunal ulceration among 29 patients within four years of operation.

It appears that only nine instances of spontaneous major gastric infarction, three of them total organ infarction, have been reported.⁶⁶⁻⁷¹ All of these patients died, even though diseases of varying degrees of seriousness were basically at fault. It is interesting to note that in one-third of the cases there was no explanatory arterial disease. In one four year old boy who had been severely burned four months before death, there was gangrene with perforations of the stomach, but all regional arteries were patent.⁷⁰ Baumann⁶⁶ described extensive arterial thrombosis but only surface infarction in a 90 year old woman, discovered incidentally at autopsy. Mallory's⁶⁹ patient developed infarction of the surgical stump following resection of the proximal half. One of Cohen's⁶⁷ patients showed gross infarction of the stomach, small bowel and half of the colon secondary to aneurysm of the abdominal

aorta, and another developed total gastric infarction due to remote venous obstruction secondary to cor pulmonale. In Platt's⁷¹ patient there was merely regional thrombosis of a tributary to the coronary vein. Others had heart disease plus aortic mural thrombi, embolism to the celiac axis from a fibrillating heart, and shock secondary to heart disease.

In brief, even though extensive dearterialization of the stomach appears to have little effect on the health of the organ or, apparently, on the course of ulcer, interference with total arterial supply or with venous return beyond some undefined point may result in death of the organ. There is a notable all-or-none character to the response to major vascular occlusion. No help in understanding of ulcerogenesis can be found here.

EMBOLISM

The best known natural mechanism for production of localized mucosal ischemia is embolization to the arterioles of the mucosa itself. The responsible emboli must obviously be very tiny, and, again, the richness of vascular anastomoses on either side of the muscularis mucosae is of such a degree that presumably a shower of occluding particles plus, perhaps, reflex arteriospasm must affect a restricted mucosal locale before ischemia can become important.

Apparently Panum⁷² made the first experimental observations. In 1862 he reported that intravenous injection of metallic mercury resulted in spotty necrosis of the gastric mucosa, as well as focal necrosis throughout many organs. Subsequently it has been found that many particulate and homogeneous substances may act as emboli experimentally: lead chromate,⁷³⁻⁷⁵ oil and fat,⁷⁶⁻⁷⁸ formalin,^{77, 78} charcoal,⁷⁹ alcohol⁸⁰ and lycopodium spores.⁸¹⁻⁸³

Study on spontaneous embolization mechanisms has suggested indirectly that subclinical mucosal infarction secondary to minute emboli may occur rather frequently.⁸⁴⁻⁸⁷ Eiselsberg⁸⁸ noted that hematemesis often follows resection of the omentum, and postulated that the mechanism must be one of retrograde embolization from ligated omental veins. Others shortly commented upon gastric ulcer and hepatic infarction following removal of the greater omentum.⁸⁹⁻⁹¹ Both Payr^{77, 78, 92} and Wilkie⁷⁹ demonstrated experimentally that the gastric mucosa is susceptible to retrograde venous embolization, by showing that ulcers and erosions can be produced merely by introducing particulate matter into the omental veins.

The possible ulcerogenic rôle of circulating fat particles is of special interest, in view of the well recognized fact that post-traumatic and post-surgical states,⁹³ particularly those which involve bone trauma⁹⁴ or bone surgery, are accompanied by lipemic showers. Both Scriba⁹⁵ in 1879 and Warthin⁹⁶ in 1913 published exhaustive studies on fat embolism, including mention of gastrointestinal effects, and their papers should be considered classics. It has been demonstrated that experimental fracture or marrow curettement in dogs and guinea pigs leads to erosion and frank ulceration of

both stomach and duodenum.^{74,76} Serial studies of gastric juice at such times have failed to provide a secretory explanation for such ulcers. That the mechanism is simply one of vascular plugging, focal ischemia, depressed mucosal resistance and autodigestion is suggested by histologic studies following intravenous injection of fat: tiny fat emboli are found in the stomach wall as well as in the lungs, brain and kidney.

Lühr⁹⁷ encountered focal embolic gastritis during gastroscopic study of two patients with multiple organ embolism secondary to bacteremia. He found oval yellow erosions ringed by red rims. This is, of course, the appearance of simple erosions or aphthous erosions; however, an embolic mechanism need seldom be considered when these common lesions are encountered.

Study of mucosal embolization has proved that the surface ischemia which is secondary to arteriolar occlusion is sufficient to permit initiation of the ulcer process. To explain "peptic" ulcer, an omnipresent mechanism which could produce the same effect must be identified.

EROSIONS

Because an erosion is an ulcer of sorts, and because a chronic "peptic" ulcer must be at an early phase of its inception, however brief, an erosion-like lesion, this minor form of mucosal dissolution has engendered much speculation in the search for ulcer etiology. A gastric or duodenal erosion may be defined as a focal loss of surface tissue extending no deeper than the glandular layer of the mucosa. Many years ago Gerhardt⁹⁸ pointed out that as a rule almost the entire lower half of the mucous membrane is still preserved, thus foreseeing recent observations that in the stomach the neck layer (junction of glands with foveolae) is the least resistant zone of the mucosa and forms the usual line of dehiscence under several types of destructive influence.

Paradoxically, the ubiquity of erosions has made study of causal associations difficult. Erosions accompany many organic lesions of the stomach—neoplasms, the many gastritides, granulomas, traumatic diseases, etc. They are encountered by the pathologist rather frequently in formerly healthy persons who have met sudden death, and by the gastroscopist in normal control subjects. On the other hand—and most important for the present argument—erosions are rarely encountered near gastric ulcers; in fact, Schindler⁹⁹ stated: "If erosions within the inflamed mucosa around an ulcer are seen, one may be practically certain that one is dealing with a malignant process." For this reason speculation has been limited largely to the isolated erosion which appears to develop spontaneously. The erosion which accompanies other organic gastroduodenal disease necessarily has had to be neglected or purposefully overlooked.

It can be stated categorically that the progression from erosion to classic "peptic" or Cruveilhier ulcer has never been observed. As a matter of his-

torical interest, one may note that both Gerhardt⁹⁸ and Langerhans¹⁰⁰ reported instances of apparent transition from erosion to ulcer, but their observations were no more than suggestive. In fact, Langerhans¹⁰⁰ was one of the first to oppose the supposition that simple mucosal erosions are merely little or young Cruveilhier ulcers, giving as his reasons localization predilections, infrequent multiplicity of ulcers, and differences in configuration between ulcer and confluent erosions. To be sure, a stomach which at one time contains a multitude of erosions may at another contain an ulcer, but the tendency for an erosive process to affect many areas of the gastroduodenal mucosa at one time renders interpretation difficult. The presence of multiple ulcers in the duodenum is unusual, and only about 5 per cent of ulcer-bearing stomachs contain more than one ulcer. Should simple erosions be pre-ulcerous lesions, it would be difficult to understand how only one might go on to full development under the influence of a stimulus which would permit other pre-ulcerous lesions to heal.

Although not conclusive by itself, this argument, plus the impressions of many observers, particularly gastroscopists who have been unable to find erosions in more than occasional instances of gastric ulcer,⁹⁹ has satisfied most interested parties that further study of the simple erosion as the anatomic basis of ulcer promises nothing. Not necessarily so with underlying causes: there may be, it has been thought, a common etiologic process at work, manifesting itself in some instances as multiple erosions and in others as "peptic" ulcer.

MUCOSAL ENGORGEMENT AND PETECHIAE

The cause of a portion of "primary" gastric erosions is rather well understood. In patients with gastrostomies and in intact subjects at gastroscopy, conditions surrounding initiation of the erosive process, as well as those encouraging healing, can be studied directly. Beaumont¹ was first to record observations on this matter, and, in fact, subsequent gastrostomy and gastroscopy studies have done little more than confirm his work. Briefly, all observers have noted that mucosa which quickly becomes engorged, especially as part of the alarm reaction, becomes particularly vulnerable to spontaneous erosion. Venous stasis and congestion affect the autoprotective mechanism at the surface quickly, so that multiple erosions may appear within an hour of capillary and venule dilatation. Under these conditions, too, the surface becomes particularly vulnerable to minor induced trauma.

Mucosal congestion may be encountered as a part of several clinical circumstances, but perhaps the most easily understood is that accompanying portal hypertension. Experience from many quarters indicates that the cirrhotic patient with esophageal varices may hemorrhage severely from gastric erosions, as well as from the varices. Apparently under these circumstances normal gastric secretory mechanisms must be intact if erosions are to de-

velop. The histologic appearance of the erosions suggests that they form not as a result of simple mechanical vascular disruption but because capillary engorgement depresses autoregulation to the acid-peptic factor. There has been satisfactory experimental reproduction of the engorgement-erosion mechanism, a good example being that of Baronofsky and Wangenstein,^{101, 102} who observed that gastric engorgement secondary to simple obstruction of the splenic vein predisposes to mucosal dissolution.

In the absence of a remote explanation for mucosal congestion, such as portal hypertension, it has been thought that local anatomic mechanisms might be responsible. In 1890 Harttung¹⁰³ explained that contraction of the muscularis mucosae may effect venous compression, with quickly developing mucosal plethora. He believed interstitial hemorrhagic infiltration to be necessary before local ischemia will permit tissue destruction. Largely because of his work the term "hemorrhagic erosion," used many years before by Cruveilhier, has persisted. Localization, however, could not be well explained by a muscularis mucosae mechanism, and simple venospasm at the submucosal level has been offered as an alternative suggestion.

If a vascular disorder which is accompanied by capillary and venous engorgement should be responsible for ulceration,¹⁰⁴ it seems reasonable to assume that petechiae would be common in the neighborhood of gastric ulcers. Possibly the antrum of the patient with duodenal ulcer might show petechiae. Data on petechiae are best obtained from gastroscopic observations; poorly understood agonal and postmortem effects on the local vasculature render autopsy studies invalid. The gastroscopic appearance of intramucosal hemorrhages is characteristic and striking enough that, if the mucosal area is visualized, they should be seen and recognized regularly.

Schindler¹⁰⁵ believed that there was a close association between petechiae and gastric ulcer, and in 1950 stated: "... The findings of mucosal hemorrhages and pigment spots seem to me characteristic of the potential ulcer stomach. If a known gastric ulcer cannot be seen at gastroscopy, the findings of localized gastric purpura permit one to state that it is probably a benign one." Schindler and Baxmeier¹⁰⁶ found purpuric changes in as many as 44 per cent of their series of 91 cases of gastric ulcer—a unique experience in the literature—as compared with an incidence of 5.6 per cent in ulcerless stomachs. Furthermore, they found correlation between the locations of the vascular lesions and the localization of the ulcers in the series, and believed this to be a potent argument for causal association. This opinion and its supporting data, however, are difficult to reconcile with Schindler's statement regarding the rarity of associated ulcer and erosions, as already quoted, because erosions and petechiae, themselves, are frequently associated, at times causally. In fact, Schindler¹⁰⁷ himself stated: "... some hemorrhages, instead of being absorbed, become ulcerated and develop into a hemorrhagic erosion. . . . I believe to have observed directly the transition of mucosal gastric hemorrhages into true gastric ulcer."

There is general agreement that traumatic petechiae do not lead to peptic ulcer, whether or not the stomach produces acid. Hemorrhagic spots are easily produced in the gastric mucosa experimentally, and morphologically these appear identical to the spontaneous type. Among a total of 240 patients, Ruffin and Brown¹⁰⁸ noted that petechiae were found gastroscopically in 65 per cent following vacuum aspiration of the gastric contents through a rubber tube, but in only 5 per cent when aspiration was omitted. They found that such lesions disappeared without erosion within a few days. When produced under gastroscopic control in a patient with a gastric fistula and with good secretory activity, the spots became brown after 10 minutes and later developed red halos. Twenty-four hours later the smaller ones had disappeared, while the larger persisted only about 48 hours. No erosions or ulcers developed.

PITRESSIN ULCERS

Because it is postulated that local ischemia may permit autodigestion and ulcer formation, it is of some interest to note the effect of the vasopressor group of drugs on the gastroduodenal mucosa, as artificial as such data may be. Pitressin causes arteriolar and capillary spasm, the degree of its effects varying much with the nature of the organ and tissue, the animal, and perhaps certain meteorologic¹⁰⁹ conditions. Objective evidence of tissue alteration may be found after single or repeated injections.^{110, 111} Nedzel¹⁰⁹ in 1938 reported that injections of pitressin readily produced gastric and duodenal ulcers in dogs, the localization tendencies being entirely similar to those of spontaneous ulcers in man. The rôle of vascular dysfunction in the process was satisfactorily proved by direct observations and serial histologic studies. Mere functional arterial spasm was found to be entirely sufficient for completion of the ulcer process, the primary factor being vascular interference with mucosal nutrition. The ulcers healed readily when relieved of vasopressor influence. Berg¹¹² demonstrated that in dogs vagotomy does not protect against acute pitressin ulcers. Later he¹¹³ presented evidence that sympathectomy affords partial protection. These findings become of particular significance when one recalls that pitressin has also an important depressant effect on gastric secretory activity.¹¹⁴ It must be borne in mind, however, that the doses of pitressin used in these experiments were greatly in excess of any ever produced in the body.

THE INTRAMURAL ARTERIOVENOUS SHUNT MECHANISM

Knowledge of the arteries which course to the stomach is one of the fundamental facts of general medical information and has received proper attention.¹¹⁵⁻¹¹⁸ After the arteries have joined the stomach, however, their fate has been assumed to be similar to that of most somatic end-arteries.¹¹⁹ Only rather recently have simple microanatomic technics been applied to a critical study of the matter. Growing appreciation of the significance of

normal native arteriovenous anastomoses throughout the body, particularly in the kidneys, has encouraged detailed investigation of these connections within the gastric wall. It would not be proper to suggest that knowledge gained along these lines has as yet resulted in solution of the ulcer problem, but one must be impressed by the possible importance of a vascular shunt mechanism in mediating primary ulcerogenic influences.

First, it is important to review a few points of gastric physiology in regard to the rate of mucosal blood flow. Automatic and induced changes in blood flow can be measured by thermal gradientometry. Briefly, the technic, as described by Richards and colleagues,¹²⁰ consists of raising the temperature of an area of mucosa in the intact stomach a few degrees above body temperature, and measuring the cooling tendency as heat is lost by conduction to blood flowing through the region. Richards made brief observations with such an apparatus, and the results were not unexpected. There was close correlation between increase in blood flow and reddening of the mucosa. With each contraction of the area being studied there was acceleration of flow, but if contraction was sustained there was then prolonged decrease in flow. Because in this latter situation there was cyanosis, the decrease was considered to be due to stasis.

Another approach to quantitation of gastric blood flow is that of plethysmography. Lim, Necheles and Ni¹²¹ attempted this with the viviperfused stomach. The technical difficulties and introduced variables render this technic of questionable usefulness.

The extensive injection and dissection studies of Djørup,¹²² published in 1922, proved rather satisfactorily that there are rich arterial anastomoses on both sides of the muscularis mucosae. Arterial disposition within the subserosa and muscularis propria differs, however, in various portions of the stomach. Along the lesser curvature, the larger arteries divide one or two times after traversing the muscle layers but before joining the submucosal plexus. The smaller arteries penetrate directly to the arterial plexus. Along the greater curvature, branches emerge regularly from the gastropiploic artery and run more directly into the deeper layers.⁵⁰ To complicate matters, the arteries which supply the gastric mucosa along the lesser curvature do not arise from the intramural plexus but have origins outside of the stomach, directly from the right and left gastric arterial chains.¹²³ After piercing the muscle layer, the arteries divide and interconnect freely to form the submucous plexus. The main network is composed of arteries measuring about 200 micra in diameter, while the anastomosing vessels measure about 50 micra. From this plexus is derived another network, the connective tissue plexus, which is separate and distinct. The connective tissue plexus lies in close approximation to the submucous plexus. The vessels intertwine, but there are no cross connections. Its vessels measure from 8 to 100 micra in diameter. They communicate freely with each other but nowhere pierce the muscularis mucosae.

In the course of studies utilizing the injection technic, De Busscher¹²⁴ in Belgium, and Bentley, Barclay and Barlow¹²⁵⁻¹²⁷ in England have made most important observations regarding native arteriovenous shunts in the stomach wall. It was observed that stomachs removed at autopsy showed a tremendous and evenly arranged network of capillaries and venules throughout the mucosa. Within the mucosa of fresh surgical specimens, however, only occasional representatives of the smaller vessels could be filled with injection mass. Quite obviously, such a result could be explained only by multiple obstructions or by a rather complete mechanism of arteriovenous shunting.

Bentley¹²⁵⁻¹²⁶ had regularly observed at laparotomy a gastric phenomenon which seemed to demonstrate a mural shunt system in action. Immediately after the peritoneum is opened, he noted, the subserosal gastric veins appear cyanotic, but as soon as the stomach is handled they become bright. Investigating, he found the oxygen saturation to be 74 per cent in these veins before the stomach had been touched, and 91 per cent a few minutes afterwards. Similar determinations in brachial venous blood showed no change. Having thus found convincing indirect evidence of a shunt mechanism, Bentley studied a stomach which had been resected under very high spinal anesthesia (T-1): upon injection of the mural arteries, the mucosal capillary pattern filled out easily. The conclusion was that the arteriovenous shunt system of the stomach operates under control of the autonomic nervous system and is called into play under certain situations of stress.

That the control mechanism, however it may act, is probably more than a simple nervous one had been suggested several years before by Lim, Necheles and Ni,¹²¹ who were unable to elicit vagus influence over the viviperfused stomach. Histamine, however, was found to increase the rate of gastric blood flow, presumably by encouraging utilization of the shunts. Babkin¹²⁸ expressed the opinion that one of the most important functions of histamine on the stomach is that exerted directly on the vasculature, an important concept from an important authority. There is a tantalizing suggestion that nitroglycerin may cause the shunts to open.¹²⁹ Flow through the shunts, as judged by perfusion of glass spheres, is much increased when epinephrine is added to the perfusion plasma.¹³⁰ The same result is elicited when a nerve accompanying the left gastric artery is stimulated electrically, even though the total flow through the stomach vessels is greatly reduced thereby.

The actual anatomy of the shunts has already been worked out in some detail.^{123-127, 130-135} When the anastomotic mechanism is thrown into use, one finds the finer vascular network of the mucosa nearly empty. The larger arteries and veins which run towards the surface at right angles from the surface of the muscularis mucosae stand out prominently. The maximal functional diameter of the shunt channels appears to be 140 micra, as judged by glass-sphere perfusion studies.¹³⁰ The minimal diameter is approximately 30 micra. Spheres 40 to 140 micra in diameter may be recovered from the venous side after being perfused through the arteries.

Barlow, Bentley and Walder,¹²³ using both microarteriography and microdissection after pigment injection, carefully followed the courses of the shunts. They found that the anastomotic vessels spring from a mucosal artery or branch thereof. Some shunt vessels are straight, others tortuous. As they course through the submucosa they become intimately entwined within the connective plexus but do not in any place join it. Either before or after piercing the muscularis mucosae, each shunt joins a mucosal or submucosal vein. The point of junction is uniformly narrowed by thickening of the vascular wall. The cells composing the thickened areas closely resemble the musculoepithelial cell of Clara. It may be assumed that they close the lumina of the shunts not by contracting but by swelling. Such an explanation would correlate well with the observation¹³⁵ that each anastomotic vessel is either completely open or closed, the amount of shunting depending upon the number of utilized anastomoses rather than upon their size. The supposition of Bentley and Barlow¹²⁷ that the mural thickening of the vessels represents a muscular sphincter mechanism is less well supported.

Bentley and Barlow were unable to demonstrate the complicated glomus type of shunt found in the kidney and previously described in the stomach by De Busscher.¹²⁴ The most recent link in the chain of evidence was forged by Herzog,¹³³ who in 1952 demonstrated functioning arteriovenous shunts near typical ulcers in human material.

COMMENT

In the search for answers to some of the important medical problems of the day, such as peptic ulcer, there is a discouraging tendency to discard investigation along simple lines in favor of very complicated biochemical or psychiatric or isotopic studies. Few investigators, for instance, appear to have any sympathy for expressed skepticism over the accuracy of the most basic of medical concepts, such as classic anatomic descriptions. The momentum of laboratory investigation does not appear to permit pause for check on the simple anatomic and physiologic matters around which a snowballing research is built. There is the feeling that clinical and laboratory understanding is so far advanced that normal human anatomy can be considered a completed science.

The history of investigation into the etiology of peptic ulcer furnishes an example of effort which at the moment seems to have been largely mispent. For several decades a tremendous amount of research has been carried out on the secretory mechanisms of the stomach because of the supposition that "peptic" ulcer must be due to peptic activity. Nevertheless, the acid-peptic factor appears to be merely a secondary or passive factor, not strictly concerned with initiation of the ulcer process. The excavation of an ulcer must be assisted by necrosis and autodigestion, but first there must be focal depression of mucosal vitality. Only an anoxic mechanism could satis-

factorily explain spontaneous focal devitalization. Although anoxia secondary to plethoric congestion and stasis is a potent source of superficial erosions, deeper and more chronic ulcerations appear to demand the anoxia of local ischemia. Some vascular diseases which might play a part have been reviewed, but it is clear that the ischemic phenomenon must be so common that it be readily available in the absence of any vascular or gastrointestinal disease—in short, the ischemic mechanism must depend on a misdirected physiologic activity.

It appears that the native arteriovenous shunt mechanism is the only means thus far demonstrated which would satisfy the mechanical criteria for production of focal ulcerogenic ischemia. That the shunting system is under humoral influence, with or without neural control, is probable. It may well be that the presence of an excessively efficient shunting mechanism is merely one of the stigmata of the ulcer patient, occurring as part of the "ulcer type" psychoanatomic complex, but being, unlike the high-arch palate or narrow subcostal angle, of actual etiologic import. Investigation is under way to elucidate the nature of this influence and means of curbing it.

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PULMONARY PARAGONIMIASIS: A REVIEW WITH CASE REPORTS FROM KOREA AND THE PHILIPPINES*

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PULMONARY paragonimiasis is a disease caused by the presence within the lung parenchyma of the oriental lung fluke, *Paragonimus westermani*. Known variously as endemic hemoptysis, lung distoma and pulmonary distomiasis, the disease was first introduced to medical science approximately 75 years ago following its recognition at the postmortem examination of a Bengal tiger. It was first reported in man in 1880.¹ There is some dispute about the existence of other species, *P. ringeri* and *P. compactus*, but apparently only minor differences have been described, and common usage has practically evolved to the preference of *P. westermani* for all forms found in man. A closely related species, *P. kellicotti*, has been found in animals on the North American continent. Animal reservoirs include the dog, cat, pig, sheep, goat, tiger, leopard, panther, wolverine, mink, mongoose, civet cat, wild cat, fox, wolf and beaver. Geographical distribution of the disease in man has been limited mainly to the Philippines, Japan, Korea and Formosa, and to some parts of China, India, South America, Africa, Nigeria, Thailand and the Malay States. Only one human infection with *P. kellicotti* has been reported in North America.^{2,3} In the American literature we were able to find reports of only seven other cases among American personnel, all of whom had been in endemic regions.⁴ It is therefore natural that interest in this disease in the United States has been no more than academic, or at most only a mere medical curiosity. The recent global war and the current conflict in Korea have exposed many of our soldiers to endemic areas. From our experiences† it seems probable that pulmonary paragonimiasis will be encountered among American soldiers and, because of its rarity, may be misdiagnosed as pulmonary tuberculosis, bronchiectasis, cystic disease of the lungs, etc. At the present time there are two soldiers recently returned from Korea who have been hospitalized for this disease, one in Fitzsimons Army Hospital, the other in the Station Hospital of Camp Carson, Colorado. Both of these patients were originally diagnosed as pulmonary tuberculosis.

It is our purpose, therefore, to invite the attention of physicians in this

* Presented at the Regional Meeting of the American College of Physicians, Denver, Colorado, February, 1953. Received for publication January 30, 1953.

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† One of us (F. T. R.) had the opportunity to observe the disease in the Philippines during a 19 year period. Also, observations were made (R. W. L. and J. C. B.) on approximately 250 cases among Korean prisoners of war in a United Nations hospital in Korea during early 1951.

country to pulmonary paragonimiasis. In addition, we shall endeavor to discuss some of the clinical features of this disease which in our opinion are inadequately or inaccurately described in current standard textbooks.

LIFE HISTORY

Large numbers of eggs are produced by the adult flukes which are harbored in cystlike burrows of the lung parenchyma. The ova escape from the body in sputum or are swallowed and excreted in stools. For continuation of the life cycle it is necessary that ova reach fresh-water ponds or rivers where, after 14 to 49 days, a ciliated miracidium emerges from each egg and invades one of several genera of snails. Within the snail, development progresses in from two to five months through sporocystic, redial and cercarial stages. Approximately 20 cercariae are thereby produced from each miracidium. The free-swimming cercariae escape from the snail and enter several forms of crabs or crayfish, the second intermediary host, where they develop into metacercariae. If unable to find a suitable crustacean host the cercariae perish in about 24 hours. It is the metacercariae, encysted in the liver, muscles and gills of crustacea, which when ingested become infective to man and other animal reservoirs.

When the encysted metacercaria enters the upper gastrointestinal tract of man its cyst wall is digested and a larval form, *adolescercaria*, emerges. This larva then penetrates the upper jejunum, traverses the peritoneal cavity, passes through the diaphragm, enters the pleural space and finally invades the lung, where maturation to the adult form takes place. Just why the *adolescercaria* displays such a preference for pulmonary tissue is not known. However, it has been found to invade all other organs with the exception of the stomach.

PATHOGENESIS

At any point along the migratory pathway between the intestine and the lung, larvae may become localized and thereby induce disease in the intestinal wall, peritoneal cavity and pleura, as well as in the lung parenchyma. However, larvae exhibit a decided predilection for pulmonary tissue, and involvement of the lungs constitutes by far the most common site of localization. Pleural effusion may occur, and in some of our cases in Korea ova were found in aspirated pleural fluid. Pleurisy, however, seems to be a relatively uncommon complaint.

Larval invasion of the lung parenchyma is accomplished by a burrowing process, with production of small tunnel-like canals surrounded by acute inflammatory reaction. These burrows terminate in cystic dilatations in which the mature flukes reside. Initially, only the outermost areas of the lung are involved in the burrowing process, but as the disease progresses the deeper portions are invaded, adjacent tunnels may coalesce and cystoidal

areas burst into small and medium sized bronchi. Fibrosis becomes apparent as the acute inflammatory stage subsides.

One might expect that bronchograms made in the presence of such burrows communicating with bronchi might closely resemble the bronchial dilatation of bronchiectasis. Such was not our experience in Korea, however. Bronchography was performed on a limited number of patients with pulmonary paragonimiasis, but no evidence of bronchiectasis or puddling could be demonstrated. This is in agreement with Bercovitz.⁵

Musgrave,⁶ working in the Philippines in 1907, reported autopsy findings in eight cases and classified the lesions into four different types: "(1) Non-suppurative, with eggs infiltrated in host tissue, leading to round cell and connective tissue reaction and usually to abscess formation; (2) tubercle-like in which the abscess may contain caseous material; (3) suppurative; and (4) ulcerative, in which healing is only partially successful." In our experience we have not encountered the tubercle-like lesions with caseation in uncomplicated pulmonary paragonimiasis. We have seen the tubercle-like lesions only in those cases which had concomitant pulmonary tuberculosis. The coexistence of pulmonary tuberculosis and pulmonary paragonimiasis was frequently observed both in the Philippines and in Korea, apparently as a result of the prevalence of tuberculosis in those regions.

CLINICAL FEATURES

The symptoms and physical findings of paragonimiasis depend upon what stage of the disease has been reached, as outlined in the pathogenesis. However, after invasion of the lung parenchyma has become fully developed the following features are characteristically found: (1) hemoptysis; (2) the presence of opercular eggs in the sputum, and (3) positive findings in the chest roentgenogram.

Hemoptysis is the predominant symptom. Intermittent, brief hemoptotic episodes are the rule, but, on the other hand, the almost daily production of rusty brown sputum for periods of weeks or even months is not unusual. In the absence of secondary infection the sputum is thin, mucoid and even watery in nature, and contains short, stringy particles of tenacious, gelatinous material. This often appears as a characteristic sediment-like material in the sputum and accounts for its rusty brown color. The particles are dark brown to reddish brown in color and have been described by others⁷ as resembling small strands of tobacco. To us their appearance was suggestive of a sandy precipitate at the bottom of the sputum cup. These particles represent aggregates of *Paragonimus* ova and are easily isolated for microscopic examination. This rusty brown material should not be mistaken for blood, although it is often mixed with streaks or flecks of blood. Sputum production, although variable, at times may quantitatively resemble that of the bronchiectatic patient. In the presence of secondary infection, the sputum may be purulent.

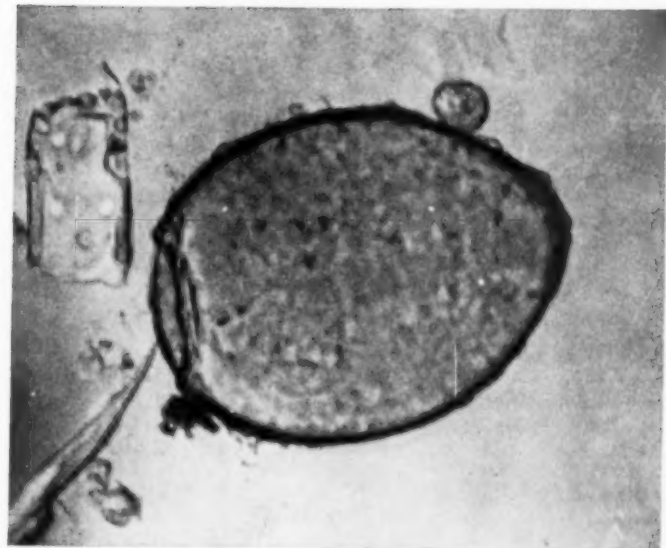


FIG. 2. High power magnification of single ovum, showing morphologic characteristics (case 2).



FIG. 1. Typical appearance of *Paragonimus* ova in unstained sputum specimen (case 2).

In a frank case of pulmonary paragonimiasis, opercular eggs are always found in the sputum (figures 1 and 2). Identification is made on examination of wet preparations of sputum. (Drying destroys the ova.) Adult parasites are only rarely coughed up in the sputum.

Shortness of breath, fever, malaise, fatigability and anorexia may be present in patients with extensive pulmonary involvement. There is no chronic cough; rather, it occurs most often only following a vague feeling of chest discomfort, and the patient coughs in a conscious effort to expel material from the lungs. In uncomplicated pulmonary paragonimiasis fever, if present at all, rarely exceeds 99° to 100° F. Other evidences of toxicity were observed chiefly in patients with other coexistent illness such as septic wounds, malnutrition, avitaminosis or other infectious disease. Toxic symptoms in such patients frequently improved or disappeared entirely with successful treatment of the complicating disease, even though hemoptysis, roentgen findings and ova in the sputum persisted unaltered. It is our impression, therefore, that uncomplicated pulmonary paragonimiasis rarely causes significant systemic symptoms, and the patient most often appears surprisingly healthy, well nourished and unaffected by the disease.

The presence of increased numbers of eosinophils in the peripheral blood has been pointed out repeatedly in standard texts and in reports of the disease. Similarly, eosinophilia was a common finding in our * patients, but most often occurred in association with other helminths, such as *Ascaris lumbricoides*, hookworm or *Clonorchis sinensis*. After antihelminthic therapy was successfully employed eosinophilia usually was absent. Similarly, the total white blood count was often normal or only slightly elevated in uncomplicated cases, and the differential count was normal or disclosed only a slight granulocytosis. Tillman and Phillips⁷ also point out that eosinophilia was not a constant finding in their cases. It was a frequent finding among the patients seen in the Philippines that the appearance of eosinophilia in the peripheral blood closely paralleled the episodes of hemoptysis, subsiding as the hemoptysis disappeared and recurring as hemoptysis again made its appearance.

RADIOGRAPHIC FINDINGS

There are no roentgenologic findings that can be considered typical of pulmonary paragonimiasis. However, the picture simulates that of pulmonary tuberculosis so closely that it would be more nearly apropos to consider Paragonimus infestation in only those chest films assumed to be tuberculosis in which tubercle bacilli cannot be found, and the patient relates possible exposure in an endemic area.

The most common picture we have found consists of a linear, patchy infiltration, with a predilection for the bases and periphery of the lung fields (figure 3). In cases with relatively recent onset of symptoms the patchy

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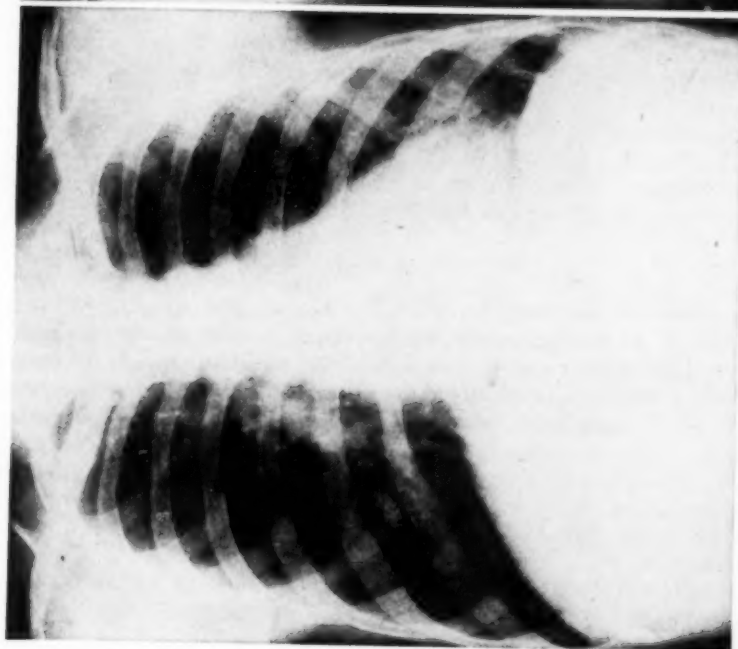


FIG. 3. Linear and patchy infiltration with predilection for lung bases, demonstrating most typical radiographic picture.

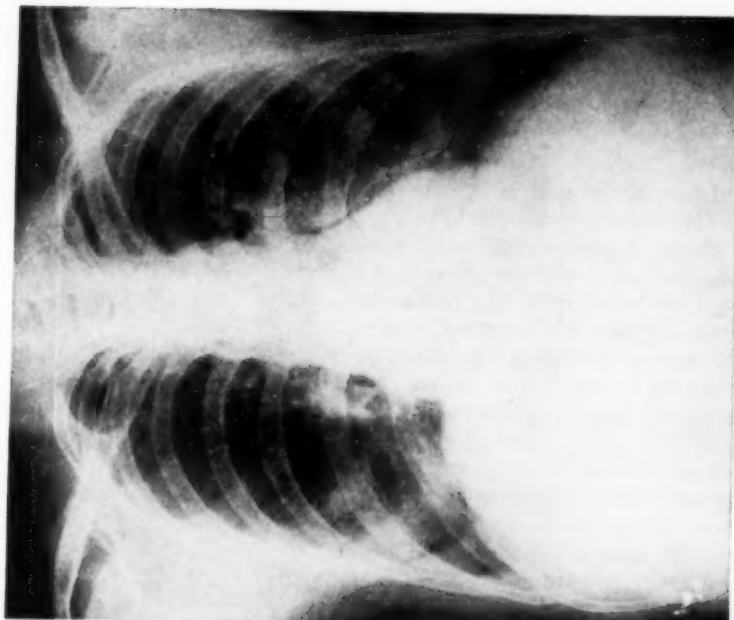


FIG. 4. Example of "exudative" phase involving right lower lung field; general condition of patient excellent. Note nodose-like lesion in fourth intercostal space anteriorly on the right.

density was not unlike that of an exudative pneumonitis which, in contrast to the more persistent fibrous type density, tended to disappear with symptomatic improvement. Another frequent finding was a well defined area of rarefaction, usually not measuring over 8 mm. in diameter, lying within a linear density. Probably the adjective "cystoidal" conveys a more accurate description than "cavitary," since it connotes the pathologic process underlying the roentgenographic findings, namely, a burrowing process by the organism with reactive fibrous tissue production (figures 4 and 5). Not only the medical officers primarily interested in diseases of the chest but also the general medical officer reviewing films in our series in Korea would point to this type of lesion occurring on a routine chest film as "pathognomonic of the fluke"; chances were excellent that, on questioning by a Korean doctor, the patient would admit typical symptomatology and ova would subsequently be found in the sputum. The relatively unchanging character of the pattern on serial radiography, combined with its association in a healthy individual with sputa persistently negative for *M. tuberculosis*, established the diagnosis with relative certainty.

Although small effusions were relatively rare, many of the chest roentgenograms demonstrated varying degrees of plastic pleuritis. Calcification was noted in some areas of density ascribed to *Paragonimus* infestation; however, a sampling of 50 tuberculin skin tests on non-patient Korean personnel in the second and third decades was, without a single exception, positive. The prevalence of tuberculosis among Koreans makes it impossible to evaluate such calcific lesions seen radiographically without parallel histopathologic examination. We are therefore unable to say whether calcification occurs in uncomplicated pulmonary paragonimiasis.

Frank cavitation could be found in only a small number of cases (figures 6 and 7). Usually, further studies eventually revealed a chronic pyogenic pulmonary abscess or, more commonly, pulmonary tuberculosis in which associated lung distomiasis was coincidental.

COURSE

The disease is extremely benign. The Korean and Filipino patients, after initial fright due to hemoptysis, become so accustomed to occasional blood spitting that after a while they attach little significance to its presence. Some patients never seek medical aid even though they have hemoptysis, and the diagnosis is made only incidentally while investigating some unrelated complaint. Secondary anemia does not usually develop even after many years of periodic blood spitting. One of the most characteristic and surprising features of pulmonary paragonimiasis is the history of intermittent hemoptysis in an otherwise asymptomatic patient who is well nourished, afebrile and free of any stigmata of chronic pulmonary disease. One of our patients in Korea distinguished himself as an outstanding athlete in spite of active pulmonary paragonimiasis. One of us (F. T. R.) has known many

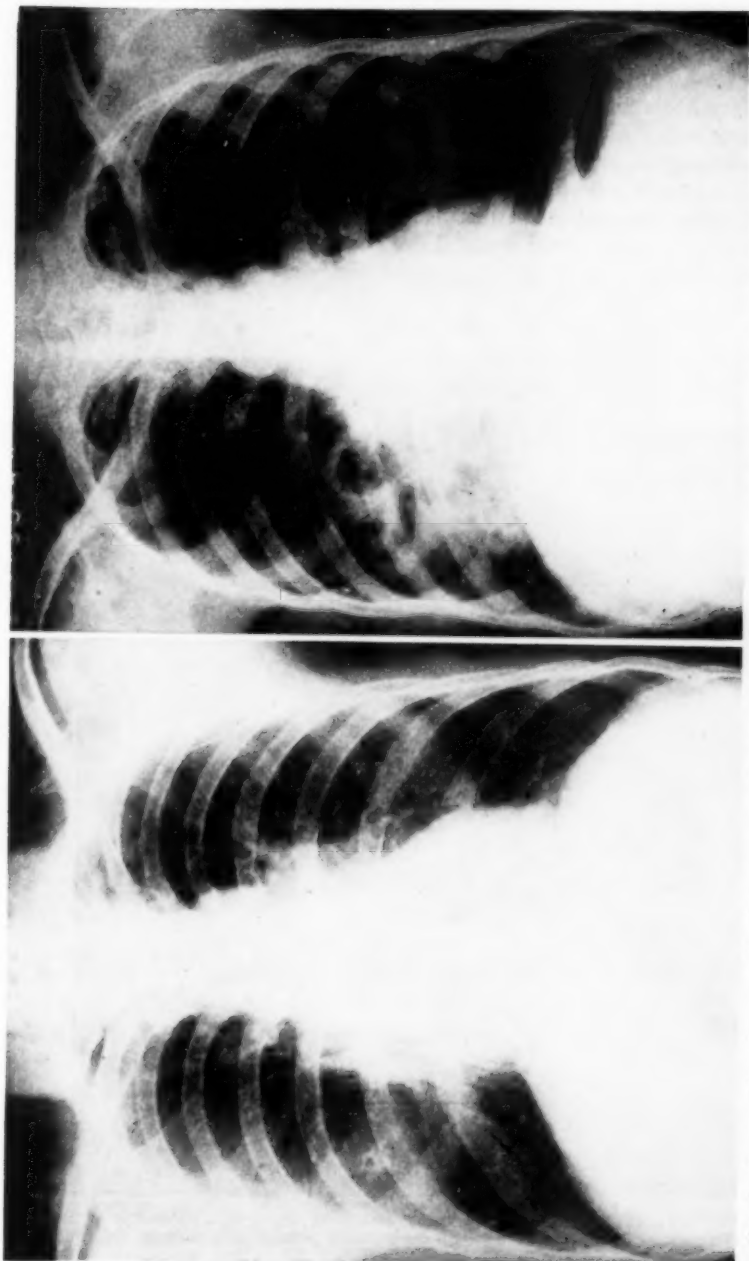


FIG. 5. Same patient four months later, demonstrating "shelling out" of nodose area on right; general condition remains excellent.

FIG. 6. Multiple abscess formation with fluid levels at right base; sputa not remarkable except for unusually heavy *Paragonimus* population.

patients who had the disease for 16 years without debility. We may add that we have yet to see an adult patient with pulmonary paragonimiasis who has died primarily from this disease, nor have we observed death due to pulmonary hemorrhage in this disease. The few adult cases we have seen at autopsy were those in whom the disease extended to the brain, liver and/or other vital organs, or those who died of some other disease.

Will a patient who has left an endemic area to live elsewhere not burn out the disease or outlive the disease? We have no categorical answer to this question except to point out that the *Paragonimus fluke* is a hermaphrodite and therefore may be able to keep on reproducing.

COMPLICATIONS

Although pulmonary lesions constitute the primary pathologic process, involvement of virtually every organ system in the body has been recorded.

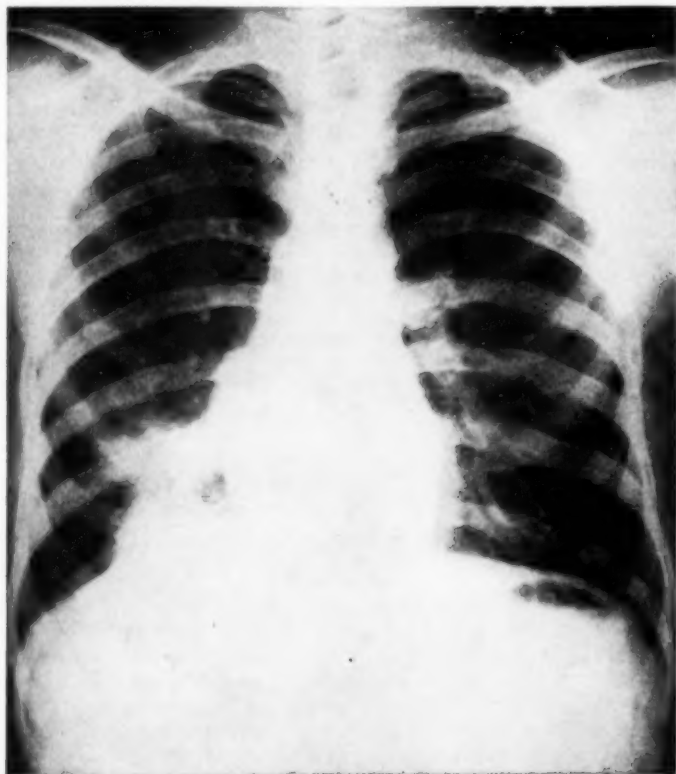


FIG. 7. Two month follow-up film (same patient as figure 6) after course of penicillin and emetine; some reduction in sputum production; patient continued to be practically symptom-free.

Musgrave⁶ found lesions in every region except the stomach. Involvement of skeletal muscle, presumably due to hematogenous dissemination, allegedly has accounted for unusual muscular aches and cramps in some cases. The formation of lesions in the gastrointestinal tract apparently is not uncommon, but infestation of the liver or other abdominal viscera is unusual in adults. In the Philippines, infants and young children not infrequently demonstrated extensive extrapulmonary involvement, particularly of the abdominal organs, in addition to extensive pulmonary lesions. Such cases were always asso-

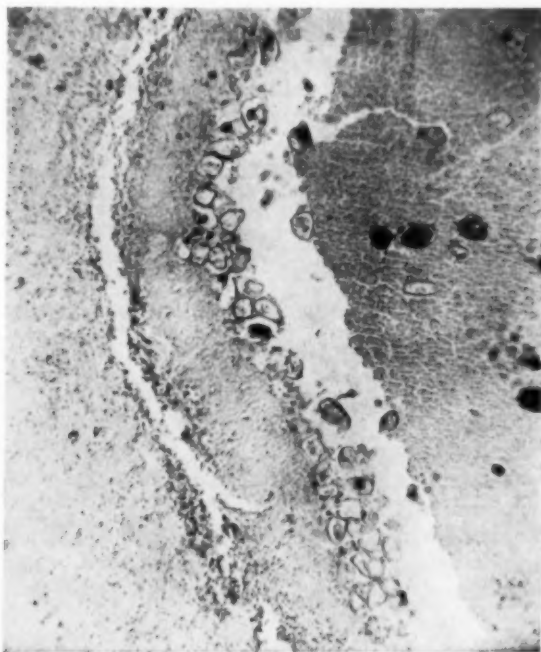


FIG. 8. Autopsy finding of extensive dissemination of ova throughout central nervous system, giving rise to encephalitis syndrome.

ciated with malnutrition or other infectious diseases, and the paragonimiasis seemed certainly to play a contributory rôle in the fatal outcome of some patients. Rarely, lesions are seen in the skin or subcutaneous tissues, and superficial abscess formation with ova in the discharged material has been described.

Our experiences with Korean patients with extrapulmonary involvement was limited to two cases with lesions of the central nervous system. One was a patient in whom the clinical diagnosis of Japanese B encephalitis was made. After running a febrile, comatose course which failed to respond to

intensive antibiotic therapy the patient died. At autopsy, multiple abscesses containing *P. westermani* ova were found throughout the brain (figure 8). The second case exhibited symptoms and signs of an expanding lesion in the right temporal lobe. A craniotomy was done and an abscess in the right anterior temporal lobe was found to contain ova of *P. westermani*.

TREATMENT

To date there is no known paragonimicidal agent. Various drugs have been tried, notably tartar emetic, emetine, lipiodol and prontosil. Several antimony compounds, arsenicals and methylene violet have been found ineffective in infected dogs.⁸ Because Fuadin was reported by Khalil and Betache⁹ to be efficacious in the treatment of another fluke-induced disease, schistosomiasis, it seemed possible that a similar response might be obtained in paragonimiasis. Accordingly, a few cases in the Philippines were treated with intramuscular Fuadin. Canizares and Celis¹⁰ have reported on the use of this drug in pulmonary paragonimiasis. Although inconclusive, results have been encouraging. Also, pneumoperitoneum for the control of profuse pulmonary hemorrhage was successfully employed in one case in the Philippines (figures 9 and 10).

In those cases seen in Korea the intermittent administration of emetine was carried out. One grain was given intramuscularly daily for six consecutive days, followed by six days of no treatment. This was followed by a second six day course of one grain intramuscularly daily. Response to this regimen initially was encouraging. Symptomatic improvement, as reflected by reduction in sputum production and hemoptysis, and by decreased numbers of ova in the sputum, was observed almost without exception. Complete disappearance of ova from the sputum and improvement in the chest roentgenogram occurred fairly frequently. However, such regression was short lived; symptoms recurred, ova again appeared in the sputum, and pulmonary infiltrations became more evident within one to three weeks after therapy was discontinued.

CASE REPORTS

Case 1. This patient, a 24 year old male Filipino, was admitted to the 10th General Hospital on April 19, 1948, because of an hemoptysis of about 6 ounces of blood. There were no associated constitutional symptoms. The chest x-ray revealed a hazy density involving the entire right apex and extending to the lower border of the second anterior rib, with a cavity 2 cm. in diameter (figure 9). The patient gave a history of having had two other episodes of blood spitting in 1946, but he did not consult a physician because he felt well and did not want to miss work. He was a native of the island of Leyte, Philippines, an endemic *Paragonimus* area.

The physical examination revealed no significant abnormalities except distant breath sounds in the right supraclavicular and apical areas. The temperature, pulse rate and blood pressure were within normal limits. Except for an eosinophilia of 15 per cent, peripheral blood examination was unremarkable; the sedimentation rate was 18 mm. in one hour. Sputum examination revealed operculated eggs of *P.*

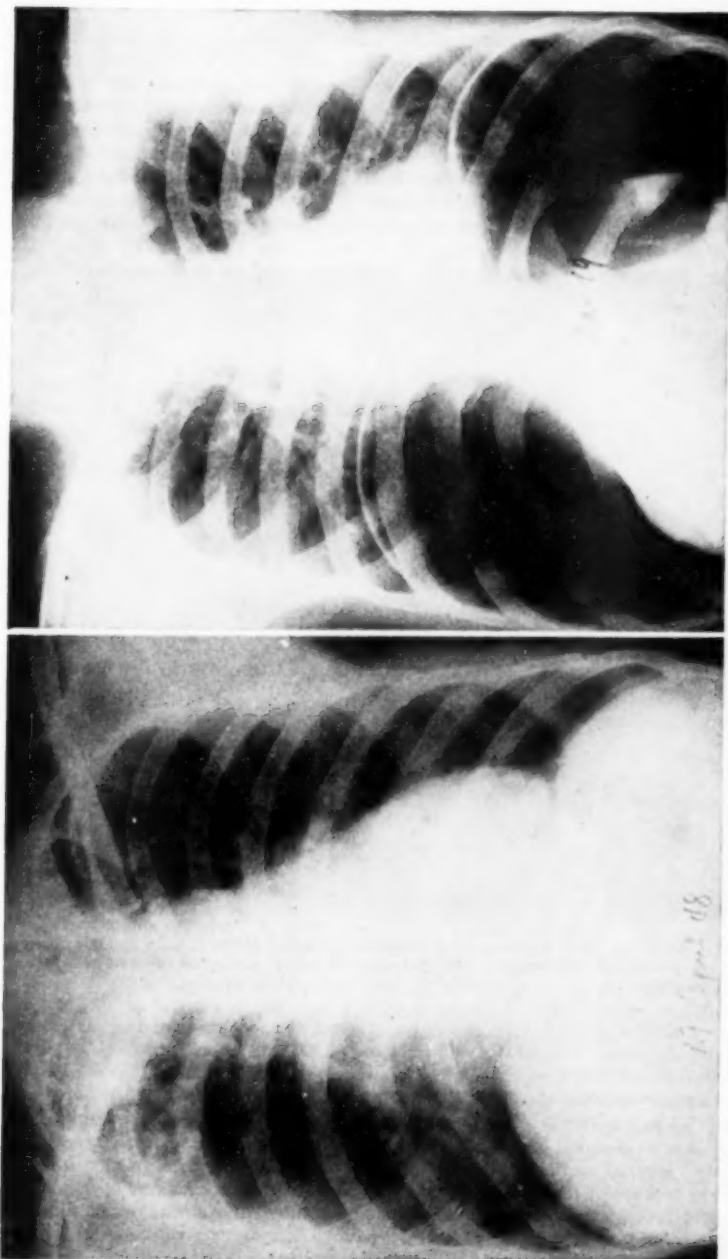


FIG. 9. Film taken at time of extensive hemoptysis, showing infiltration and cavitation in right upper lobe (case 1); sputa repeatedly negative for tubercle bacilli.

FIG. 10. Same patient nearly one year later at time of refill of a pneumoperitoneum, showing marked regression of lesions. Throughout this period sputa were consistently positive for Paragonimus ova and just as consistently negative for acid-fast bacilli.

westerni. Acid-fast bacilli were never demonstrated in repeated sputum smears and cultures. The patient was treated with Fuadin on April 22, 1948, with the following regimen: 1.55 c.c. on the first day; 3.5 c.c. on the second day; 5 c.c. on the third day, and 5 c.c. every other day for six more doses. On April 24, 1948 another, more profuse hemoptysis occurred, and in an effort to control the hemorrhage a pneumoperitoneum was induced (figure 10). A third hemoptysis occurred on April 26. Throughout this period the patient was afebrile and had no complaints.

After May 15, 1948, *Paragonimus* eggs could no longer be found in the sputum. The patient was then discharged from the hospital and was treated as an outpatient for refills of pneumoperitoneum. He received a second course of Fuadin from May 21

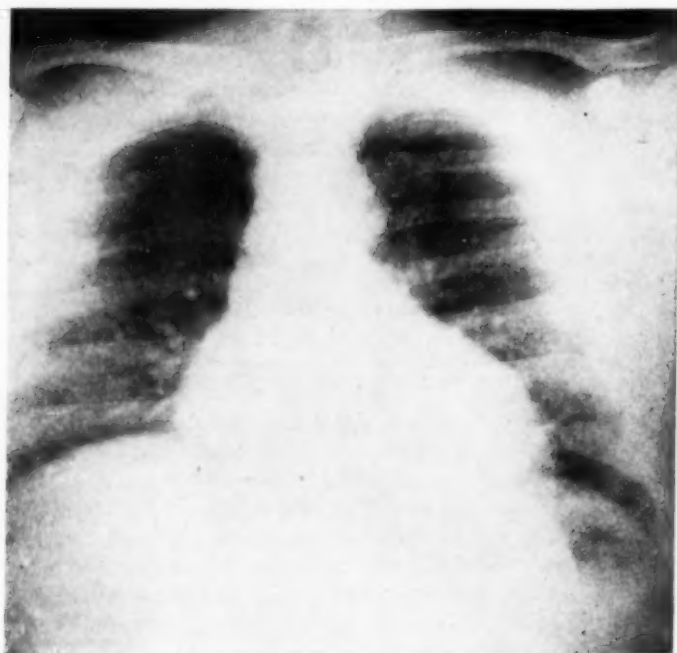


FIG. 11. An apical view, demonstrating minimal left apical lesion in case 2; little change over one year period of observation, with persistently heavy *Paragonimus* ova population in sputa.

to June 4. Subsequent chest films showed a gradual disappearance of the cavity and a progressive decrease in extent of infiltrations. The chest film on March 4, 1949, revealed infiltrations in the right upper lobe (figure 11). The patient did not return for further follow-up after March, 1949.

Case 2. The patient, a 42 year old male Filipino-American, was admitted to Fitzsimons Army Hospital on November 14, 1951. He was transferred from the U. S. Army Hospital in the Philippine Islands, where he had been hospitalized on July 25, 1951 because of soft exudative infiltrations in the left apex found on a routine chest x-ray. A tentative diagnosis of pulmonary tuberculosis was made and on September 15, 1951 blood was noted in the sputum. On further questioning he ad-

mitted that he had been spitting some blood during the preceding two weeks but had not reported this to the doctor because he was afraid he might lose his privilege to go out on passes. Serial sputum examinations for acid-fast bacilli were negative. The patient was transferred to Fitzsimons Army Hospital with the diagnosis of minimal pulmonary tuberculosis. Physical examination was essentially negative, and the patient was found to be asymptomatic. All efforts to find acid-fast bacilli in the sputum and gastric washings were unsuccessful. Diagnostic bronchoscopy and bronchograms revealed no significant abnormalities. However, the patient continued to have intermittent mild cough productive of a moderate amount of sputum. Second strength P. P. D. was positive, and skin tests with coccidioidin and histoplasmin were negative. The patient was placed on a trial of combined streptomycin and para-aminosalicylic acid in February, 1952. On February 18, sputum examinations revealed operculated ova of *P. westermani*. Streptomycin and PAS were therefore discontinued. Because of the finding of Paragonimus eggs the patient was questioned carefully concerning his eating habits. He admitted having eaten raw fish and, less often, raw crabs in Hawaii, where he had moved at the age of 10 and grown to manhood. He had never had hemoptysis in Hawaii. He joined the Army in 1944. The first episode of blood spitting was in Okinawa in 1949, at which time he coughed up about 30 c.c. of blood. He reported to sick call but a chest film was not taken at that time. He was told that the blood probably came from the gums and teeth. A year later he had a recurrence of hemoptysis; a chest film revealed no significant abnormality, and he was sent back to duty. He was sent to Korea in 1950 and performed combat duty for 11 months. The patient denied having eaten raw fish or crabs while stationed in Okinawa, Japan and Korea. However, while in Korea during combat he was forced to drink water he obtained from streams without benefit of purification.

The patient gained 10 pounds in weight and continued to feel well during three courses of Fuadin. Throughout therapy, however, ova persisted in the sputum, although they became appreciably fewer in number.

DISCUSSION

According to Stitt,² fresh water crustacea are eaten raw in Japan but not in Korea. However, other texts³ disagree with this statement, as do our recent experiences with Korean prisoners of war. Presumably as a result of the influence of Japanese occupation, Koreans do eat such crustacea, which are uncooked or partially pickled in alcoholic beverages. Indeed, such preparations are regarded by many Koreans as a delicacy. Heating the crustacea to 55° C. or higher kills the metacercariae and therefore prevents infection.

We wish to emphasize that our experiences with pulmonary paragonimiasis have been almost entirely of a clinical nature: observations at the patient's bedside, sputum and peripheral blood examinations, and changes in the chest roentgenogram. Pathologic specimens have been too limited to warrant a more comprehensive review of the disease processes. This limitation, it is felt, is a natural result of the benign nature of pulmonary paragonimiasis, most opportunities for pathologic study arising as a result of coexistent complications which gravely alter the prognosis. Indeed, it is this feature of the disease which has motivated our questioning the production of caseation as described by Musgrave.⁶ His pathologic studies

were made in regions where pulmonary tuberculosis was widespread, yet no attempt was made in his study to exclude the possibility of pulmonary tuberculosis coexisting with pulmonary paragonimiasis. Our observations in similar locales where both diseases are common revealed their frequent simultaneous occurrence.

Standard textbooks and reviews of the epidemiology and life cycle of *P. westermani* repeatedly reiterate the necessity of the second intermediary host. It has been suggested that the encysted metacercariae may perhaps be ingested via contaminated streams and ponds as minute particles of necrotic material containing particles of infested crustacea which have died and undergone disintegration.¹ Another possibility is the existence of another, as yet unrecognized, second intermediary host of almost microscopic size which may be ingested unconsciously in drinking water. The first suggestion seems more probable. In the Philippines many patients were seen with pulmonary paragonimiasis who, even after repeated questioning, positively denied having eaten uncooked crustacea, although they admitted drinking water from streams and wells without benefit of boiling or any other form of purification. Such cases were seen, though infrequently, in Korea as well. This observation is in agreement with the statement in Manson-Bahr: "The supposition is that the crustacean phase is not always a biological necessity."¹ Craig and Faust² are of the same opinion, and Ameel¹¹ successfully transferred the disease from one animal to another directly without passing through intermediate hosts.

SUMMARY

1. Hemoptysis in any patient with the proper geographic history should suggest the possibility of pulmonary paragonimiasis. With the recent global war and the present Korean conflict, it is anticipated that this disease will be encountered in American personnel who have been in endemic areas.

2. Paragonimiasis is usually contracted in the human by the ingestion of raw or poorly cooked fresh water crustaceans such as crabs and crayfish. The crustacean vector as an absolute biologic necessity has been questioned, and our clinical experience indicates that the disease may be obtained by the ingestion of contaminated drinking water.

3. It is questioned whether tubercle-like lesions and caseation-necrosis are caused by the fluke in pulmonary paragonimiasis.

4. Pulmonary paragonimiasis will usually be manifested by the triad: hemoptysis, positive roentgenogram of the chest, and operculated *Paragonimus* ova in the sputum.

5. There is considerable doubt whether eosinophilia of the peripheral blood is a characteristic feature of uncomplicated pulmonary paragonimiasis.

6. The clinical evolution of paragonimiasis is characterized by its chronicity and surprising benignity in spite of the persistently recurrent hemoptysis and x-ray findings.

7. The roentgenographic findings in pulmonary paragonimiasis closely mimic those in pulmonary tuberculosis.

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TRIETHYLENE MELAMINE IN THE TREATMENT OF LYMPHOMAS AND OTHER NEOPLASTIC DISEASES *

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THE usefulness of nitrogen mustard (HN_2) in the palliative treatment of certain lymphomas has become well established since the original trials in 1942.¹ More recently, a nitrogen mustard-like preparation, triethylene melamine (TEM) has been found to have therapeutic effects somewhat similar to those of nitrogen mustard itself. This new compound possesses the practical advantages, as contrasted with nitrogen mustard, of being effective by mouth, producing less nausea and little or no vomiting, obviating the necessity of hospitalization during treatment and providing a compound with prolonged effect well suited to spaced maintenance therapy.

The structural formula of triethylene melamine, chemically 2, 4, 6-triethylenimino-s-triazine, is shown in figure 1. Its reactivity with actively proliferating tissues, such as lymphoid structures and the bone marrow, is attributed to its ethylenimino groups, which are similar to the ethylenimonium hydrolysate of nitrogen mustard, methyl (β -chloroethyl) amine, which forms when it is dissolved in water.² Triethylene melamine was discovered to possess inhibiting effects upon experimental tumors and upon mouse leukemia late in 1949.^{3,4} In the first clinical report of this agent, in May, 1950, Rhoads et al. found temporary improvement could be produced in patients with Hodgkin's disease, lymphosarcoma and chronic lymphocytic and granulocytic leukemia, and in mycosis fungoides.⁵ Results from other investigators have since been reported.^{6, 7, 8, 9, 10}

This present report deals with 38 patients with Hodgkin's disease, lymphosarcoma, leukemia or other neoplastic disease, who have received triethylene melamine orally since September, 1950, when this study was commenced.

METHODS

Triethylene melamine was administered orally as 5 mg. scored tablets. The drug was given with 150 c.c. of plain water after the patient awoke in

* Received for publication November 18, 1952.

Read before the southeastern regional meeting of the American College of Physicians, Havana, Cuba, November 7, 1952.

A preliminary report of 17 of the 38 cases in this series was read before the annual meeting of the Southern Section of the American Federation for Clinical Research, New Orleans, January 26, 1951.

Triethylene melamine was furnished through the courtesy of Dr. John Rueggesser, Medical Director, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

the morning, and breakfast was then withheld for one hour. Outpatients were given only the number of tablets required for the prescribed doses before the next scheduled visit.

The schedule of administration and total dose of TEM varied considerably from patient to patient, depending upon such factors as the diagnosis, stage, duration and major sites of the disease, the general condition of the patient, previous treatment, bone marrow function, and the possible presence of hypersplenism or other complications. Some patients deemed potentially sensitive to the drug were first given a test dose of 5 mg., with determination of the blood count and platelet count in one week before proceeding with further treatment. Examples of other schedules used, depending upon circumstances, were 5 mg. a day for two to six doses on consecutive days, 2.5 mg. every other day for three to eight doses, 5 mg. a week for four to six doses, and 2.5 mg. to 10 mg. every three to six weeks as maintenance therapy. In

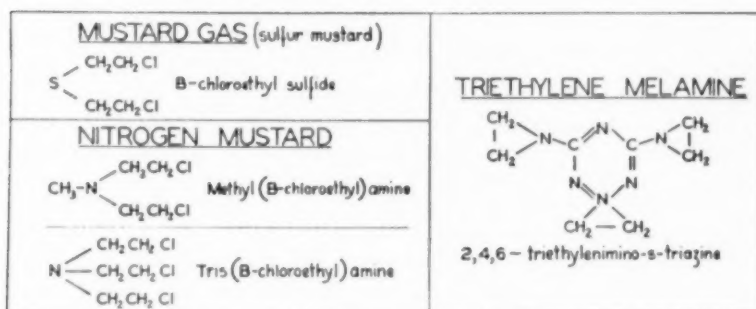


Fig. 1. Comparison of the structural formulas of mustard gas, methyl (β -chloroethyl) amine and triethylene melamine.

general, patients with Hodgkin's disease may tolerate the largest dose, and those with reticulum cell sarcoma and myelogenous leukemia also often require and tolerate sizable total doses. In lymphosarcoma somewhat smaller amounts may be effective, while patients with chronic lymphocytic leukemia may obtain a good therapeutic effect from relatively small doses which have the additional advantage of being small enough to avoid serious bone marrow depression.

Of the 38 patients in the series, 27 remained in hospital while receiving TEM and for at least three weeks after beginning its administration, four were given this agent both as hospital patients and as outpatients, and seven were treated entirely as outpatients. Blood counts and platelet counts and bone marrow examinations were performed on all patients before treatment. Blood and platelet counts were determined at least twice a week on hospital patients, and on every visit of outpatients before they received a further dose. A second bone marrow examination was performed seven to 35 days after

TABLE I
Therapeutic Effect of Triethylene Melamine

	Excellent	Good	Slight	None	Total
Hodgkin's disease	2	7	5		14
Reticulum cell sarcoma			1	3	4
Lymphocytic lymphosarcoma	1		1	1	3
Follicular lymphosarcoma	1				1
Leukemia, lymphocytic, chronic	1	2		1	4
Leukemia, lymphocytic, acute			1		1
Leukemia, granulocytic, chronic		1		2	3
Leukemia, granulocytic, subacute		1	1		2
Leukemia, granulocytic, acute				1	1
Carcinoma, bronchogenic		1		1	2
Carcinoma, oat cell, of lung			1		1
Carcinoma, squamous cell, of larynx				1	1
Melanosarcoma, metastatic				1	1
Total					38

therapy was completed in 14 of the 38 patients. Outpatients were usually seen once a week during active treatment, and at intervals never greater than three weeks, even while maintenance doses of TEM were being taken. Treatment was necessarily highly individualized, since succeeding doses of TEM depended upon whether remission was induced or whether bone marrow depression limited or precluded further therapy. X-ray therapy was used in combination with TEM when deemed beneficial, and blood transfusions, antibiotics and other supportive measures were employed as indicated.

Table 1 summarizes the therapeutic effect of TEM, and table 2 lists the individual response to treatment of the 38 patients in the series. All diagnoses were established by biopsy or by bone marrow aspiration.

HODGKIN'S DISEASE

Fourteen patients with Hodgkin's disease were treated with oral triethylene melamine. Eleven of these had previously been treated with roentgen-rays or nitrogen mustard. The general condition of these patients was classified as poor in seven, fair in four, good in two and excellent in one. The average duration of disease from the onset of symptoms to beginning of TEM therapy was 48 months. First evidence of improvement was noted at an average of nine days after the first dose of TEM was given. The duration of improvement was 30 days on the average following each course of TEM therapy. This interval of improvement, persisting after any one course of TEM treatment, varied from as little as four days in a patient who was terminal, to 35 days in a more favorable case. That improvement was not maintained for longer intervals from a single course was probably a

TABLE II
Summary of Response to Treatment of 38 Patients Given Triethylene Melamine Orally

Case No. Age Sex	Diagnosis; Stage or Major Sites; Duration	Previous Therapy and Response	General Condition	Dosage Schedule	Time Between Courses	Total Dose mg.	Response to Triethylene Melamine	Day of First Evidence of Improvement and the Improvement Duration	Thera- peutic Effect of TEM	Length of Follow-up Period
1 52 M	Hodgkin's disease; generalized; severe; 24 months	None	Poor	5 mg./d X 4 5 mg./d X 3 5 mg./d X 1	54 days 34 days 32 days	55 mg.	Good responses were obtained with each of 3 courses, with decrease in temperature to normal, improved appetite, decreased malaise and slight increase in splenomegaly and hepatomegaly. At the end of the 4th course of TEM the patient still had a rapid downward course with high fever and with a thrombocytopenia and hemorrhagic manifestations developing one week before death.	2nd; 28 4th; 24 6th; 19 None	Good	6 months (died)
2 27 F	Hodgkin's disease; generalized; 33 months	Röntgen, good initially, poor recently	Poor	5 mg./d X 4 5 mg./d X 2 5 mg./d X 3	44 days 74 months	45 mg.	Rapid control of fever, malaise, nausea and anorexia was obtained after the 1st and 2nd courses in this patient with far-advanced disease. Moderate decrease in size of the spleen and peripheral lymph nodes also occurred. Less effect was evident from the 3rd course.	3rd; 28 4th; 25 14th; 14	Excel- lent	134 months (died)
3 35 M	Hodgkin's disease; mediastinum, right lung, abdomen and generalized; 3½ years	Röntgen, good previously, poor recently	Very poor (terminal)	10 mg./d X 1 5 mg./q other day X 4 5 mg./d X 1 5 mg./q other day X 5	7 days 5 days 54 days	60 mg.	Following the 1st course there was slight lessening of the degree of splenic compression and also of a cor pulmonale but this was temporary. No benefit from the 2nd course was observed. Subsequently, HNs produced brief but definite alleviation of compression symptoms.	20th; 12 Inconclusive	Slight	44 months (died)
4 25 F	Hodgkin's disease; generalized; 4 years	Röntgen, good; HNs excellent	Poor	5 mg./d X 3 5 mg./q other day X 3 5 mg./q other day X 3	5 months 34 months	45 mg.	Good response, with gain in weight and appetite and control of fever, was obtained with each of the 1st and 2nd courses. No improvement was observed following the 3rd course.	4th; 35 7th; 14 None	Good	14 months (died)
5 36 M	Hodgkin's disease; mediastinum, left lung, liver and generalized; 5 years	Röntgen, good initially, very poor recently; HNs good	Poor	5 mg./d X 3 5 mg./d X 1 5 mg./q other day X 4 2.5 mg./2 other day X 2	11 months 1 week 23 days	45 mg.	No diminution in size of a large mediastinum was observed from TEM alone initially. However, 2 months after TEM was first given, this patient which had previously been found unresponsive to x-ray decreased about 50% in size following further x-radiation. Subsequent courses elicited no significant response. Jaundice which developed shortly before death was attributed to extreme parenchymal liver involvement at post mortem.	30th; 28 Inconclusive None	Good	24½ months (died)

TABLE II—Continued

Case No. Age Sex	Diagnosis; Stage or Major Sites; Duration	Previous Therapy and Response	General Condition	Dosage Schedule	Time Between Courses	Total Dose	Response to Triethylene Melarsine	Day of First Evidence of Improvement and the Duration	Therapeutic Effect of TEM	Length of Follow-up Period
6 27 M	Hodgkin's disease; generalized; 12 months or more	None	Very poor	2.5 mg./d X 3 2.5 mg./d X 5	48 days	25 mg.	Only slight temporary decrease of a high spiking temperature and of malaise, without noticeable effect upon the enlarged lymph nodes. Patient died suddenly after a convulsion 82 days after TEM first started, for this rapidly progressive Hodgkin's sarcoma.	4th; 7 5th; 4	Slight	82 days (died)
7 26 M	Hodgkin's disease; left inguinal abdomen; 2 years	Röntgen, good	Good	5 mg./d X 3 5 mg./d X 2	7 days	25 mg.	Complete disappearance of large abdominal masses and disappearance of leg edema; the enlarged retroperitoneal lymph nodes, were observed.	5th; 39	Excellent	39 days
8 34 M	Hodgkin's disease; inguinal nodes; 1½ years	None	Excellent	5 mg./d X 4		20 mg.	Enlarged inguinal and femoral nodes, which clinically were the only site of involvement, regressed rapidly to ½ their former size. With no further treatment other than 1,600 R to each groin, lymph nodes regressed. Patient remained asymptomatic with no lymph node enlargement at 15 months.	7th; 35	Good	15 months
9 31 M	Hodgkin's disease; mediastinum, liver and generalized; 2 years	Röntgen, excellent; HN; excellent	Fair	5 mg./d X 5 5 mg./d X 3	42 days	40 mg.	Good clinical improvement with subsidence of fever, malaise and hiccoughs as well as moderate decrease in size of an enlarged liver, of mediastinal nodes and of peripheral lymph nodes followed the 1st course. Similar abolition of fever occurred after a 2nd course 42 days later.	6th; 30 8th; not determined	Good	48 days
10 61 M	Hodgkin's disease; chiefly of abdomen; also generalized; 6½ years	Röntgen, good formerly; poor recently	Poor	2.5 mg./d X 4		10 mg.	Slight transient clinical improvement and a moderate decrease in an abdominal lymph node mass took place. Improvement of uremia, due to bilateral hydronephrosis, occurred after a large abdominal node, followed TEM, with a decrease of the blood urea N from 45 to 25 mg. $\%.$ Per-sistent thrombocytopenia, limited therapy at this time. Moderate temporary improvement was obtained 2 months later with intravenous nitrogen mustard.	7th; 10	Slight	96 days (died)

TABLE II—Continued

Case No. Age Sex	Diagnosis; Stage or Major Sites; Duration	Previous Therapy and Response	General Condition	Dosage Schedule	Time Between Courses	Total Dose- age	Response to Triethylene Melamine	Day of First Evidence of Improvement and the Improvement Duration	Therapeutic Effect of TEM	Length of Follow-up Period
11 28 F	Hodgkin's disease; mediastinum, left lung and abdomen; 54 months	Röntgen, good initially; recently	Fair	5 mg./q wk. X6 5 mg./q other day X6	7 months	60 mg.	Mediastinal nodes and left lung lesion decreased in size following 1st course. Mediastinal mass and night sweats reduced after 2nd course.	21st; 2 months 15th; 14 months	Good	15½ months
12 24 F	Hodgkin's disease; left lung, mediastinum, ribs; 47 months	Röntgen, good	Fair	2.5 mg./d X2		5 mg.	Prompt relief of rather severe pain over cervical, dorsal and lumbar regions and lower right anterior ribs followed the 1st course. Although the response was subjective it appeared valid.	2nd; not determined (over 1 month)	Good	1 month
13 36 M	Hodgkin's disease; mediastinum and abdomen; 41 months	Röntgen, good	Good	5 mg./d X2 5 mg./d X2	1 week	20 mg.	Only a slight decrease in the size of a moderately large abdominal mass was noted, as well as slight diminution in size of a few moderately enlarged axillary and supraclavicular lymph nodes.	12th; 21	Slight	7½ months
14 36 M	Hodgkin's disease; neck, abdomen and generalized; 6½ years	Röntgen, fair	Fair	2.5 mg./d X3 2.5 mg./d X3	5 days	15 mg.	Only slight decrease in temperature and slight decrease in size of an abdominal mass occurred after TEM but this mass was later more responsive to x-ray therapy than formerly.	7th; 10	Slight	2 months
15 53 M	Reticulum cell sarcoma; mediastinal, mediastinum, ribs, right pubis; 2 years or more	Röntgen, good	Poor	5 mg./d X3 5 mg./d X2	1 week	25 mg.	No diminution in size of a lymph node mass of the left neck was observed, and x-ray therapy was given elsewhere.	None	None	30 days
16 16 M	Reticulum cell sarcoma; mediastinum; 8½ months	Röntgen, none	Poor	5 mg./d X5		25 mg.	Slight, transient improvement was evidenced by considerable decrease in dyspnea, cough and weight loss. Slight decrease in size of a large mass causing tracheal compression.	5th; 6	Slight	20 days (died)
17 35 M	Reticulum cell sarcoma; both lungs, mediastinum, abdomen, skin and generalized; 5 months	Röntgen, very poor; HNA, very poor	Very poor (terminal)	5 mg./q other day X6		30 mg.	No significant effect was noted from the TEM therapy. Patient's course was unusually rapidly downward.	None	None	27 days (died)

TABLE II—Continued

Case No. Age Sex	Diagnosis; Site or Major Sites; Duration	Previous Therapy and Response	General Condition	Dosage Schedule	Time Between Courses	Total Dose	Response to Triethylene Mélamine	Day of First Evidence of Improvement and the Improvement Duration	Thera- peutic Effect of TEM	Length of Follow-up Period
18 48 M	Reticular cell sarcoma; mediastinum and generalized; 31 months	None	Poor	5 mg./q other day X5 5 mg./q other day X5	18 days	50 mg.	No clinical improvement and no regression in the size of the mediastinal mass were noted at any time from TEM or deep x-ray to the mediastinum (1956 R). Died 27 days after TEM started.	None	None	27 days (died)
19 50 M	Lymphocytic lymphoma; peripheral lymph nodes; 25 months	Röntgen, response not known	Fair	5 mg./d X1 5 mg./d X1	4 days	20 mg.	No favorable or adverse effects were noted during 22 days of daily follow-up. However, 2 weeks later (36 days after starting TEM) the bone marrow and blood showed infiltration with lymphoblasts and a rapid downward course ensued. Died 64 days after TEM commenced.	None	None	64 days (died)
20 40 F	Lymphocytic lymphoma; mediastinum, right lung, abdomen; 24 months	Nitrogen mustard, good; roentgen, poor recently	Poor	5 mg./q week X3	1 week	15 mg.	Slow, only moderate, transient decrease in the size of a rather large abdominal lymph node mass took place. When x-ray therapy was again directed to the mass the response to roentgen therapy, although only fair, was somewhat better than before TEM treatment. Persistent leukocytosis and leukopenia were limiting factors in treatment.	21st, 24	Slight	31 months (died at 13 months)
21 50 M	Lymphocytic lymphoma; peripheral lymph nodes, especially cervical, axillary and inguinal; 7 months	None	Excellent	5 mg./d X3		15 mg.	Definite regression in the size of enlarged peripheral lymph nodes was evident by the 4th day and some nodes were decreased to less than one-fourth of their original size when last measured 28 days after TEM was started.	4th; not determined (over 28 days)	Excellent	28 days
22 38 F	Follicular lymphoma; abdomen primarily; also mediastinum; 20 months	Röntgen, good	Excellent	5 mg./q 6 days X4 2 1/2 mg./d X4 2 1/2 mg./d X4 2 1/2 mg./d X4	16 months 4 months 4 months	50 mg.	From the 1st course a good response was noted with rather rapid diminution in size of an abdominal mass. The 3rd course was successful in relieving bone pain in the humerus. The 4th and 5th courses were combined with roentgen therapy and were effective in shrinking abdominal and mediastinal nodes (with the 2nd course) and in relieving root pain of the lower dorsal region (with the 4th course).	6th; 68 days not evaluated as x-ray also given. 5th, bone pain relieved but not evaluated. 7th day; not evaluated as x-ray also given	Excellent	22 months

TABLE II—Continued

Case No. Age Sex	Diagnosis; Stage or Major Sites; Duration	Previous Therapy and Response	General Condition	Dosage Schedule	Time Between Courses	Total Dose	Response to Triethylene Melamine	Day of First Evidence of Improvement and the Improvement Duration	Therapeutic Effect of TEM	Length of Follow-up Period
23 5 M	Lymphocytic leukemia, chronic; over 2 years	Koentgen, good	Fair	2.5 mg./d 3rd day X3 5 mg./d 7th day X2	11 days	17.5 mg.	Weight gain, increased strength, control of fever and decrease in spleen size followed TEM therapy. A rapid decrease in leukocytes from 920,000 per cu. mm. to lower levels occurred.	10th; 2 months	Good	9 months (died)
24 32 M	Lymphocytic leukemia, chronic; 2 years	None	Fair	5 mg./d X2 2.5 mg./d X2	3 weeks	15 mg.	Improvement in well-being and a moderate decrease in spleen size occurred.	7th; 35 days	Excellent	35 days
25 73 M	Lymphocytic leukemia, chronic; probably 4 years	None	Poor	5 mg./d X5		25 mg.	Diminution in size of an enlarged liver, spleen and lymph nodes was observed, and abdominal ascites attributed to enlarged abdominal nodes and a part to liver involvement was abolished.	None	None	28 days
26 86 M	Lymphocytic leukemia, chronic; duration not known	None	Good	5 mg./d 1 other day X3		15 mg.	A moderate decrease in size of enlarged cervical, axillary, inguinal and femoral nodes as well as of the spleen occurred.	10th; over 30 days	Good	30 days
27 54 M	Lymphocytic leukemia, acute; 6 months	Amethop- terin and cortisone, poor	Very poor (terminal)	2.5 mg./d X4 2.5 mg./d X4	12 days	20 mg.	Partial alleviation of fever, night sweats and a moderate improvement of malaise promptly and transiently occurred after each course.	2nd; 8 days 3rd; 5 days	Slight	25 days
28 43 M	Granulocytic leukemia, chronic; 14 months	Koentgen, good	Fair	5 mg./d X1 5 mg./d X1 5 mg./d X1	8 days 7 days 7 days	20 mg.	No immediate beneficial or deleterious effects were observed. Leukemia became acute shortly before death which occurred 46 days after TEM was started.	None	None	46 days (died)
29 43 M	Granulocytic leukemia, chronic; 2 years	None	Good	5 mg./d X3 5 mg./d X2	8 days	25 mg.	Persistent left sciatica, believed due to leukemic infiltration; was completely relieved of pain two days after treatment was started. The subsequent course has been favorable.	2 days; not determined	Good	24 months
30 46 F	Granulocytic leukemia, chronic; 11 months	Koentgen, fair	Fair	5 mg./d X5		25 mg.	No significant clinical improvement in leukocyte count occurred. Maximum drop in the white cell count occurred 14 days after TEM was started.	None	None	18 months (died)
31 27 M	Granulocytic leukemia, subacute; 8 months	None	Poor	5 mg./d X5 5 mg. X1	55 days	30 mg.	Rapid reduction in size of spleen and lymph nodes and general clinical improvement after the 1st course. Treatment improvement followed a 2nd small dose.	3rd; 3 weeks 16th; 2 weeks	Good	7 months (died)

TABLE II—Continued

Case No. Age Sex	Diagnosis; Stage or Major Sites; Duration	Previous Therapy and Response	General Condition	Dosage Schedule	Time Between Courses	Total Dose mg.	Response to Triethylene Melamine	Day of First Evidence of Improvement and the Improvement Duration	Therapeutic Effect of TEM	Length of Follow-up Period
32 26 M	Granulocytic leukemia, subacute; 8 months	None	Poor	2½ mg./d X4		10 mg.	Only slight improvement noted with decrease in temperature and improvement in appetite for a period of 10 days. A progressive downward course was resumed with fever, generalized petechiae, scattered ecchymoses and slight further enlargement of the liver, spleen and peripheral nodes. Died 24 days after TEM started.	5th, 10 days	Slight	24 days (died)
33 56 M	Granulocytic leukemia, acute; 42 days	Urethane, no response	Very poor (terminal)	2.5 mg./d X4 2.5 mg./q other day X3	7 days	17.5 mg.	No demonstrable improvement was noted. Continued fulminating downward course and died 41 days after TEM started.	None	None	41 days (died)
34 59 M	Bronchogenic carcinoma; right lung, vertebrae; 6 months or more	X-ray, fair; IHN, good	Fair	5 mg./d X2		10 mg.	Gradual relief of severe root pain from T8-10, after TEM. But no decrease in size of the lung tumor was noted.	16th, 4 weeks	Good	17½ mos. (died)
35 59 M	Bronchogenic carcinoma; right lung, vertebrae; 8 months or more	None, except light lobectomy	Poor	5 mg./d X5		25 mg.	No definite improvement and no relief of severe root pain due to metastases to D 7-10 was observed.	None	None	32 days (died)
36 44 M	Oat cell carcinoma; right lung; 3½ months	None	Fair	5 mg./d X4 2.5 mg./d X5	35 days	32.5 mg.	No objective improvement could be demonstrated other than a slight decrease in the amount of atelectasis of the right upper lobe 2½ weeks after the last course. No relief from bone pain due to metastases was noted.	9th, 10 days	Slight	86 days
37 57 M	Squamous cell carcinoma; larynx, left cervical nodes; 1½ years	Röntgen, fair	Poor	5 mg./d X6		30 mg.	None.	None	None	2 mos.
38 44 M	Melanosarcoma; mediastinum, right leg, axilla, rib, adrenal gland, cervical nodes; 15 months	None, except excision of cervical nodes	Fair	5 mg./d X5		25 mg.	Further skin involvement was seen to take place and no regression was noted on serial chest x-rays.	None	None	55 days (died)

reflection of the moderate doses of TEM used, as well as the scheme employed of ordinarily not giving further doses as maintenance until signs of relapse could be observed and recorded. The average total dose was 30 mg. of TEM, administered in one or more courses over an average follow-up period of eight months. The therapeutic response (table I) was considered excellent in three patients, good in six and slight in five patients. Five patients have died, and each was rapidly approaching the terminal stage at the time TEM was started. While the response of Hodgkin's disease to TEM

TABLE III
Clinical Comparison of Intravenous Nitrogen Mustard and Oral Triethylene Melamine

	Nitrogen Mustard (Intravenous)	Triethylene Melamine (Oral)
Total dose per course, average adult	20 to 30 mg. (.4 mg./kg.)	10 to 40 mg.
Dose range	10 to 60 mg.	5 to 75 mg.
Duration of treatment	1 to 6 days	3 to 30 days
Side effects		
Extravasation	Severe local reaction	None
Venous thrombosis	Occasional	None
Nausea and vomiting	Both are usual	Nausea often; vomiting only occasionally
Ease of administration	Requires hospitalization	Patient may be ambulatory
Maintenance therapy	Rehospitalize to treat relapses	Well adapted to oral maintenance doses
Dosage control	Safe with usual dose due to extensive experience	Dosage varies more by oral route; treatment must be more prolonged to safely deliver maximum therapeutic dose
Bone marrow depression		
Time to peak depression duration	5 to 15 days shorter	12 to 50 days or more longer
Severity	Usually less, is more predictable	Usually greater, is less predictable
Peripheral blood alterations	Moderate leukopenia is common	Leukopenia, anemia, and thrombocytopenia are often greater than with HN ₂ and this is especially true of thrombocytopenia
Therapeutic effects (see text for details)	Qualitatively approximately similar in Hodgkin's disease and lymphosarcoma. Has faster, less prolonged action	Therapeutic spectrum is broader since it extends to leukemia, especially the chronic lymphocytic variety. Has slower, more prolonged action

is seen to be quite variable in degree, it correlated primarily with the stage of the disease and with the dosage schedule utilized from patient to patient.

Constitutional symptoms, such as malaise, weakness, fever, night sweats, pruritus and anorexia, were partly relieved in all 14 patients and completely relieved in four patients for variable intervals of time. In three patients (cases, 3, 5 and 11), areas of disease that had become x-ray resistant were found to be again responsive to x-ray therapy after a course of TEM. In one patient (case 10) in uremia due to bilateral hydronephrosis secondary to extensive abdominal lymph node enlargement, temporary improvement followed TEM administration with a decrease of the blood urea nitrogen from

75 to 25 mg. per cent. A similar response to TEM in a comparable patient with leukemia has been reported.¹¹

CASE REPORTS

Case 1 (figure 2). Hodgkin's Disease. This 52 year old married former diesel engineer (T. L.) was admitted to the Veterans Administration Hospital, Coral Gables, on June 16, 1950, with a history of fever for three weeks, a dry, hacking cough for six months, gradual weight loss from 174 to 152 pounds over the past year, and malaise of almost two years' duration.

Examination showed a rather pale, febrile, chronically ill man with a persistent hacking cough. There was slight enlargement of the right axillary, both inguinal and

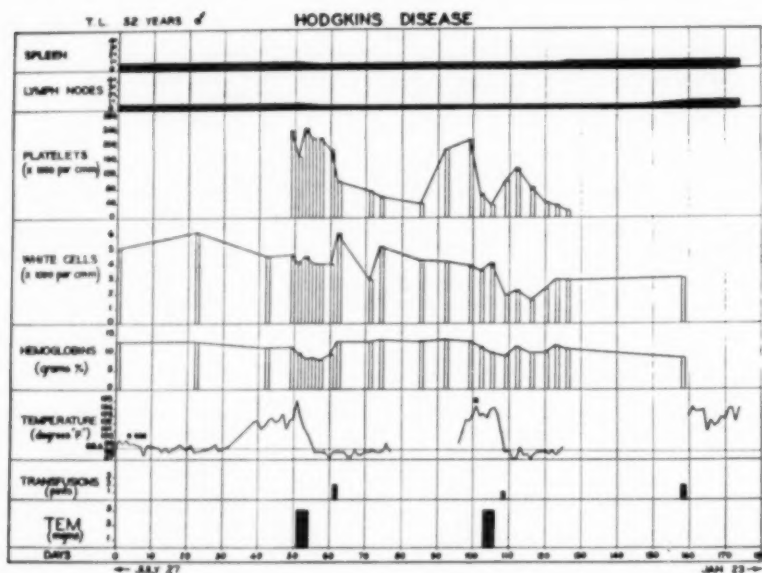


FIG. 2. Case 1. Hodgkin's disease, far advanced, showing response of temperature and course after oral treatment with TEM.

both femoral node groups, and a firm spleen tip was palpable two fingerbreadths below the left costal margin. Many medium moist inspiratory râles were heard at the right base posteriorly and laterally. The blood pressure was 84/60 mm. of Hg, and it remained in a low range (below 100 systolic) throughout his course. No abnormal pigmentation of the skin or mucous membranes was seen. The hemoglobin was 11.5 gm. per cent; red cells, 3,870,000 per cubic millimeter; hematocrit, 38.0 per cent; platelets, 240,000 per cubic millimeter; white cells, 6,550 per cubic millimeter, with an essentially normal white cell differential. The Kepler-Power water test was abnormal, with a night volume of 375 c.c., a maximal hourly volume of 88 c.c., and A equal to 16.5. The eosinophil test of Thorn was also abnormal, with 112.5 per cubic millimeter initially and 150.0 per cubic millimeter four hours after 25 mg. of ACTH. The chest x-ray showed mottling in the region of the phrenic sinus of the right lower lung field,

which was interpreted as an area of pneumonitis with fibrous pleurisy. Bronchoscopy revealed a normal tracheobronchial tree. Bone marrow examination was not remarkable; it showed no multinucleated cells of the Reed-Sternberg type. Biopsies of lymph nodes from the right axilla and left epitrochlear regions were not diagnostic, but a left axillary node showed the pathologic changes of Hodgkin's disease.

Prior to treatment the patient ran an unremitting fever with a slowly downward course. However, after each of the first three courses of TEM (5 mg. a day for four doses; 5 mg. a day for three doses, 54 days later; 5 mg. a day for three doses, 68 days later), the temperature quickly returned to normal, appetite was improved and ma-

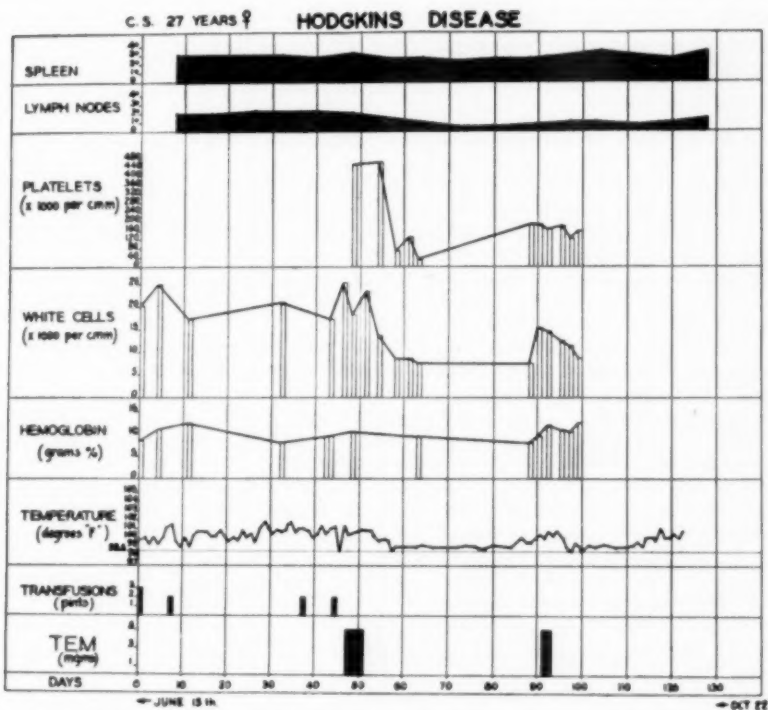


FIG. 3. Case 2. Hodgkin's disease, far advanced, showing response of temperature and leukocytosis and course after oral treatment with TEM.

laise decreased. Only a slight decrease in hepatomegaly and splenomegaly occurred. The platelet level was considerably decreased after each of these courses. At two and one-half weeks after the third course of TEM the patient again developed a high fever of Pel-Ebstein type, required transfusions of about 500 c.c. of blood each week, and showed a slow gradual drop in the platelet count to a level of between 20,000 and 40,000. Bone marrow examination revealed moderate hypoplasia of the nucleated elements, with a moderate increase in degenerating cells and a slight increase in lymphocytes and plasma cells. Trials of cortisone and of ACTH were relatively ineffective in combating bone marrow depression. During the last week of life the patient had epistaxis, bleeding from the gums, hematuria and rectal bleeding; he

developed moderate jaundice and generalized ecchymoses of the skin and died on March 16, 1951. Autopsy revealed approximately 600 c.c. of clotted blood in the stomach, bloody fecal material throughout the intestines, petechial, submucosal and serosal hemorrhages throughout the intestinal tract, pin-point or small hemorrhages in all organs, infiltration of both adrenals with the Hodgkin's process, considerable retroperitoneal lymph node enlargement, especially along the aorta, a liver that weighed 2,875 gm. and a spleen of 750 gm.

Comment: This case illustrates the favorable therapeutic effect of TEM on each of three separate occasions in a patient with far advanced Hodgkin's disease. It also calls attention to the marrow depression which is to be expected, at least to a limited extent, after the use of this drug. This depression may become especially important where impairment in marrow reserve is already present.

Case 2 (figure 3). Hodgkin's Disease. This 27 year old single female (C. S.), formerly of the Women's Army Corps, was first seen at the Veterans Administration Hospital, Coral Gables, on November 21, 1949, complaining of a lump in the neck and of easy fatigability and malaise.

In September, 1947, a diagnosis of Hodgkin's disease was made by lymph node biopsy from the base of the right neck at the Lahey Clinic, and x-ray therapy to the right neck and mediastinum was given. In November, 1948, and again in July, 1949, she received x-ray therapy to the spleen, and on each occasion increasing fatigue, anorexia and weight loss were ameliorated.

The patient was re-admitted June 13, 1950, with a recrudescence of her previous complaints of weakness, easy fatigability, malaise, fever, anorexia and intermittent nausea and vomiting. She appeared pale, thin and gaunt, and weighed only 88 pounds. The spleen extended five fingerbreadths below the left costal margin, the liver edge extended two fingerbreadths below the right costal margin, and moderate generalized enlargement of peripheral lymph nodes was present. The hemoglobin was 8.5 gm. per cent; red cells, 3,250,000 per cubic millimeter; platelets, 460,000 per cubic millimeter; white cells, 20,850, with an essentially normal differential. X-rays of the chest and long bones were normal.

During the first six weeks in hospital the patient continued to go downward slowly and to lose weight, with no treatment other than blood transfusions at frequent intervals. However, within three days of beginning TEM on August 1, 1950 (dose: 5 mg. a day for four doses), her temperature became normal, intermittent vomiting stopped and she began to gain a few pounds. Similar good effects took place after a second course, beginning on September 15, 1950 (dose: 5 mg. a day for two doses). Less response was seen after a third course, on May 5, 1951 (dose: 5 mg. a day for three doses), shortly after enlarged retroperitoneal nodes first made their appearance. Following the first course a precipitous drop in platelets occurred, from which recovery to about half the pretreatment level subsequently took place. The patient was subsequently lost to follow-up and died 13 months later, on September 7, 1951.

Comment: This case illustrates the repeated remissions that may be obtained in a patient with Hodgkin's disease responsive to TEM, even though the disease is far advanced.

LYMPHOSARCOMA

Four patients with reticulum cell sarcoma, three with lymphocytic lymphosarcoma and one with follicular lymphosarcoma are included in this group of eight patients.

All four patients with reticulum cell sarcoma were in poor condition, showed multiple foci of disease and were rapidly entering a terminal phase. No favorable effect could be observed in three of these patients, one of whom had previously shown very poor response to both x-ray therapy and HN₂. Slight, transient improvement was manifested by one patient (case 16) in a terminal stage, when dyspnea was considerably but temporarily relieved coincident with a slight decrease in size of a large mass compressing the trachea. Although this patient had so far shown no response to a course of x-ray therapy completed three weeks previously, the roentgen radiation may nevertheless have potentiated the small apparent response noted after TEM was given. Three of the four patients died within a month of beginning TEM, and the fourth patient was lost to follow-up.

One patient (case 21) with lymphocytic lymphosarcoma, with a seven months history and no previous treatment, showed a striking decrease in size of large cervical lymph nodes with a total dose of 15 mg. of TEM. A second patient with lymphocytic lymphosarcoma (case 20) showed only slight improvement following a total dose of 15 mg. of TEM given in three doses one week apart, and died 13 months later; but this patient was in poor condition, with generalized disease, and also had previously responded poorly to roentgen radiation. The third patient with lymphocytic lymphosarcoma (case 19) showed no immediate favorable or adverse effects after receiving 20 mg. of TEM in divided doses over a period of seven days. However, 36 days after the first dose of this agent, the bone marrow and blood showed large numbers of lymphoblasts, the rapid downward course of the acute stage of lympholeukosarcoma ensued, and the patient died 64 days after TEM was commenced. A similar sequence of events was observed in one other patient of the series (case 28), in whom a chronic granulocytic leukemia was observed to become acute, with the patient dying 46 days after TEM was started. The question of whether TEM might have played a rôle in the development of the acute phase of the disease in these patients is purely speculative.

Case 22. Lymphosarcoma. This 38 year old housewife (M. C.) was well until February, 1949, when she experienced severe low back pain accompanied by a swelling in the left epigastrium. The pain was so great that a dissecting aneurysm of the abdominal aorta was first considered, but retrograde pyelograms taken later showed considerable displacement of the left kidney. Exploratory laparotomy on April 4, disclosed an irregular nodular mass involving the entire mesentery of the small intestine. A biopsy was taken and the patient was referred to the Memorial Hospital Center for Cancer and Allied Disease, New York, where she was under the care of Dr. Lloyd Craver. At this hospital the biopsy specimens were interpreted as follicular lymphosarcoma.

On examination on April 27 at Memorial Hospital, beneath a left pararectus scar, there was felt a fusiform, firm, immovable, lobulated, slightly tender mass which filled the entire periaortic region, extending beneath the right costal margin and laterally beneath the left costal margin and measuring 10 by 7.5 inches. The patient was thereupon given x-ray therapy to the abdominal mass, which regressed rather rapidly until by September 23, 1949 it could no longer be definitely felt. Chest films at this time disclosed an increase in width of the mediastinum at the level of the aortic knob on the

right, without parenchymal or pleural involvement, and the patient was accordingly given several x-ray treatments to the mediastinum, with good response. No enlarged peripheral nodes were found other than one in the right supraclavicular and another in the left supraclavicular region, both of which regressed promptly to normal size following one x-ray radiation to each. The liver and spleen were not enlarged at this time.

This patient continued to do well from December 20, 1949, when she was first seen by one of us (O. W. B.), until October, 1950, when enlargement of the treated, somewhat indurated area of the abdomen was noted. She had lost about five pounds of weight over the preceding six weeks, her appetite had decreased, and she had developed a low grade fever. The spleen tip was just palpable, and there was no enlargement of the liver or of any peripheral lymph node group.

Following is a record of the decrease in size of the abdominal mass following the first course of TEM therapy:

Date	TEM	Abdominal Mass
10/22/50	5 mg.	5½" × 6¼"
10/28/50	5 mg.	4½" × 3½"
11/ 3/50	5 mg.	—
11/ 9/50	5 mg.	—
11/16/50	—	2" × 3"
12/29/50	—	1½" × 2½"
2/ 6/51	—	2" × 2½"
3/20/51	—	3½" × 4"
4/15/51	—	3½" × 4"

As indicated above, some shrinkage of the mass was noted after six days, and it was observed to be smallest 68 days after TEM was started. This mass later proved to be unusually sensitive to x-ray therapy, inasmuch as it promptly regressed to its former smallest measurement one month after limited x-radiation was commenced on April 15, 1951. Also observed following this course of TEM therapy were the disappearance of low grade fever, improvement in appetite, a weight gain from 118 pounds before treatment to 124.25 pounds 68 days after treatment, and slight decrease in size of the spleen to the point where the tip was no longer palpable.

A second course of TEM (2.5 mg. a day for four doses) was given 16 months later, together with local x-ray therapy, to shrink enlarged abdominal and mediastinal lymph nodes. A third course of TEM (2.5 mg. a day for four doses), administered four months later, was successful in relieving bone pain due to involvement of the head of the left humerus. A fourth course of TEM (2.5 mg. a day for four doses) was taken four months after the preceding one to obtain relief from radicular pain involving T 7-8 on the right, which had not been relieved by several trials of x-ray therapy alone.

This patient's condition remained satisfactory until recently, when she developed temporary bone marrow depression of moderate degree following recent short courses of both x-radiation and TEM at 21 months after initial TEM therapy. With the help of cortisone (total dose: 775 mg. over 12 days) and the first blood transfusions this patient had ever received (total volume: 2,000 c.c. over three days), the blood count recovered from its lowest values of hemoglobin, 6.8 gm. per cent; red cells, 2,165,000 per cubic millimeter; white cells, 1,250 per cubic millimeter; platelets, 83,095 per cubic millimeter (indirect wet method), to levels six weeks later of 14.6, 4,250,000, 2,600, and 110,000, respectively. At the present time, 23 months after TEM was initially administered, there is no sign of exacerbation of her disease, the mediastinal nodes, peripheral nodes and liver are not enlarged, and the spleen tip is barely palpable.

Comment: This case of follicular lymphosarcoma illustrates the therapeutic value of TEM not only when used alone but especially its desirable

effects when employed as a supplement to x-ray therapy. In this patient TEM appeared to enhance the effect of x-ray radiation and also helped relieve bone pain and nerve root pain on several occasions.

CHRONIC LYMPHOCYTIC LEUKEMIA

Four patients with chronic lymphocytic leukemia were treated with TEM. Of this number, the response was considered excellent in one, good in two and without favorable result in one. Beneficial effects observed were improvement of such constitutional symptoms as malaise, fever and anorexia, decrease in size of an enlarged spleen and liver, and reduction of blood and

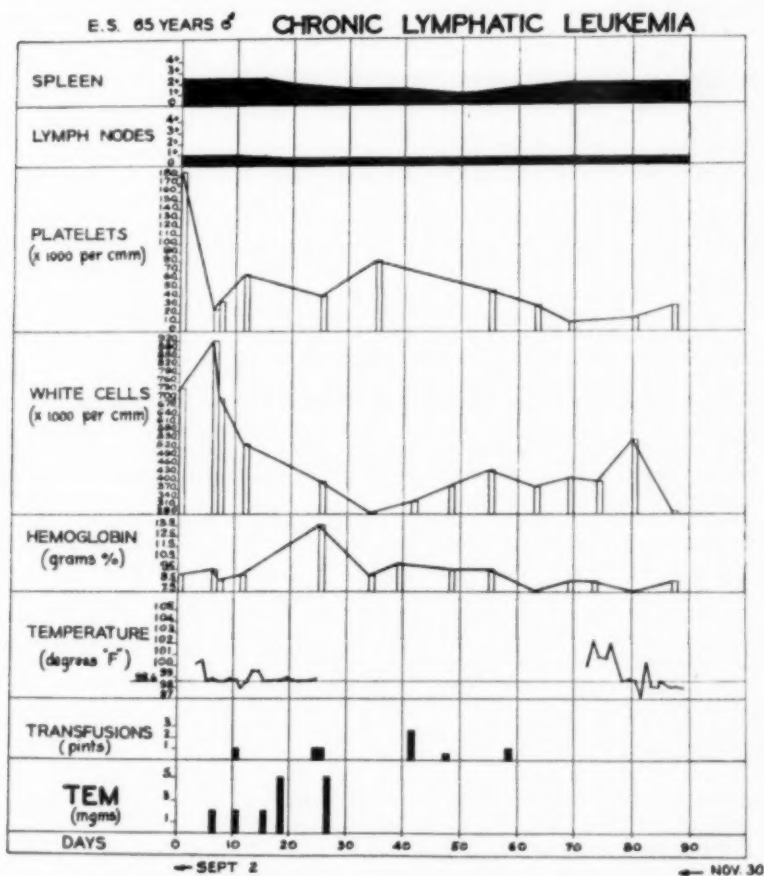


FIG. 4. Case 23. Chronic lymphatic (lymphocytic) leukemia, late stage, showing response of leukocytosis, onset of thrombocytopenia and course after oral treatment with TEM.

marrow lymphocytosis. The patient showing no improvement (case 25) was a 73 year old colored man whose general condition was poor because of considerable leukemic marrow infiltration and abdominal ascites. Neither the blood transfusion requirement of 500 c.c. each week nor the ascites, which was attributed in part to encroachment of enlarged abdominal nodes upon the venous return and in part to liver involvement, was significantly influenced during the 28 days this patient was followed. It is believed that more favorable results would have been obtained had it been possible to follow and treat the patients of this group over a longer period.

Case 23 (figure 4). Chronic Lymphocytic Leukemia. This 65 year old retired musician (E. S.) was first admitted to the Veterans Administration Hospital, Coral Gables, on November 28, 1949, because of progressive weakness and easy fatigability and a 15 pound weight loss over the past year. At that time the spleen tip was down two fingerbreadths below the left costal margin, the liver and peripheral lymph nodes were not enlarged, and the white cell count was 890,000 per cubic millimeter, with 97 per cent adult lymphocytes. A diagnosis of chronic lymphocytic leukemia was established by examination of the bone marrow, which showed extensive infiltration with adult lymphocytes. Following a course of x-ray therapy to the spleen the patient gained 30 pounds in weight and the leukocytosis was controlled for a considerable period.

The patient was re-admitted on September 5, 1950, because of recurrence of a considerable leukocytosis, which was accompanied by weight loss of eight pounds over a two month period, low grade fever and increasing easy fatigability. On examination the spleen extended five fingerbreadths below the left costal margin, the axillary nodes were moderately enlarged, and the nodes of the neck and groin regions were slightly larger than normal. The liver edge was at the right costal margin, and no petechiae or ecchymoses were seen. The left ventricle was slightly enlarged, there was a grade 3 systolic murmur at the apex transmitted to the axilla, the blood pressure was 140/72 mm. of Hg, and there were no signs of myocardial insufficiency. The hemoglobin was 10.5 gm. per cent; red cells, 3,520,000 per cubic millimeter; platelets, 178,000 per cubic millimeter; white cells, 920,000 per cubic millimeter, with 97 per cent adult lymphocytes. X-ray of the chest showed slight prominence of both hilar shadows (thought to be due to enlargement of hilar nodes) and an increase in lung markings on the left.

With the administration of TEM in a total dose of 17.5 gm. over a period of 17 days there was a decrease in the white cells from a peak of 920,000 per cubic millimeter to considerably lower levels. Maximal decrease in the white cell count was to 280,000 per cubic millimeter 26 days after TEM was commenced. Accompanying this decrease, the platelets dropped from an initial level of 178,000 per cubic millimeter and remained in a dangerously low range thereafter, despite repeated trials of ACTH and cortisone. The patient improved clinically, with gain in strength, abolition of a low grade fever, slow gain in weight, considerable decrease in spleen mass and slight diminution in size of moderately enlarged peripheral lymph nodes.

Over the following months the patient was subjectively in fairly good health except for easy fatigability, but he continued to require about 500 c.c. of blood every 14 days, and his platelet count remained in the low range of 20,000 to 40,000 per cubic millimeter. No evidence of hemorrhagic tendency was noted other than a few scattered petechiae over the legs and over pressure points. However, on June 10, 1951, following a sore throat of one week's duration, he suddenly developed shortness of breath, tachycardia, chills and fever, quickly went into severe pulmonary edema, showed widespread skin ecchymoses, commenced slow bleeding from the gums and nose, and died the following day. Autopsy revealed multiple petechial hemorrhages throughout the

body, without large hemorrhages in any location; quite marked lymph node enlargement within the thorax and abdominal cavity, but especially along the aorta; partial necrosis of both adrenal glands; a liver weighing 2,650 gm. and a spleen of 1,420 gm., both of which showed considerable leukemic infiltration; and pulmonary edema and congestion, with left ventricular hypertrophy, calcific aortic stenosis and mitral insufficiency.

Comment: This case illustrates some of the beneficial effects obtainable with TEM in chronic lymphocytic leukemia. It also emphasizes the necessity of using the drug cautiously in this disease to avert as much as possible adding to the thrombocytopenia and anemia so often encountered in the late stages.

CHRONIC GRANULOCYTIC LEUKEMIA

Three patients with chronic granulocytic leukemia were treated with TEM. One previously untreated patient (case 29) with persistent left sciatic neuritis believed due to leukemic infiltration was completely relieved of pain two days after TEM was started. This patient's subsequent course has been favorable while on maintenance urethane, and a limited course of x-ray therapy is only now being given, 24 months after commencing TEM. The other two patients, whose condition was only fair when treated, derived no significant benefit from TEM. One of these (case 28) died 46 days after TEM was started, with an acute leukemia which both clinically and hematologically had its onset only about five days before death.

ACUTE AND SUBACUTE LEUKEMIA

One 54 year old man (case 27), in a terminal phase of acute lymphocytic leukemia, experienced partial but definite alleviation of fever, night sweats, cough and malaise with each of two 10 mg. courses of TEM, and died 25 days after this agent was commenced. Another 56 year old man (case 33), whose condition was almost terminal from acute granulocytic leukemia, continued an unaltered, rapid downward course and died 41 days after the agent was first administered.

Two patients with subacute granulocytic leukemia were given TEM. Slight benefit was noted in one. A good but temporary therapeutic response was seen in the other patient, who is reported below.

Case 31 (figure 5). Subacute Granulocytic Leukemia. This 27 year old deep sea diver (J. B.) entered the Veterans Administration Hospital, Coral Gables, on July 25, 1950, with a two month history of weakness and fatigue and a 20 pound weight loss. Pain in the left thigh, due to an enlarging hematoma, had been present for 10 days. Sore throat and hoarseness had continued for the past week.

Examination showed a rather pale man, appearing chronically ill. Numerous small spider angiomas were scattered over the upper anterior chest, and one was present on either side of the bridge of the nose. The cervical nodes were only slightly enlarged, but the axillary, inguinal, femoral and epitrochlear nodes were all moderately enlarged. The spleen tip extended three and one-half fingerbreadths below the left costal margin. The liver was not enlarged. A soft systolic murmur was present at

the apex but the heart was not enlarged. A few inconspicuous ecchymoses over the lower legs were seen. No petechiae and no palmar erythema were noted. Pterygia were present bilaterally.

The hemoglobin was 9.9 gm. per cent; red cells, 3,050,000 per cubic millimeter; hematocrit, 28.0 per cent; platelets, 82,500 per cubic millimeter; white cells, 15,950 per cubic millimeter; myeloblasts, 18 per cent; progranulocytes, 6 per cent; myelocytes, 23 per cent; metamyelocytes, 12 per cent; band cells, 10 per cent; segmented cells, 15 per cent; lymphocytes, 5 per cent, and monocytes, 11 per cent, with numerous

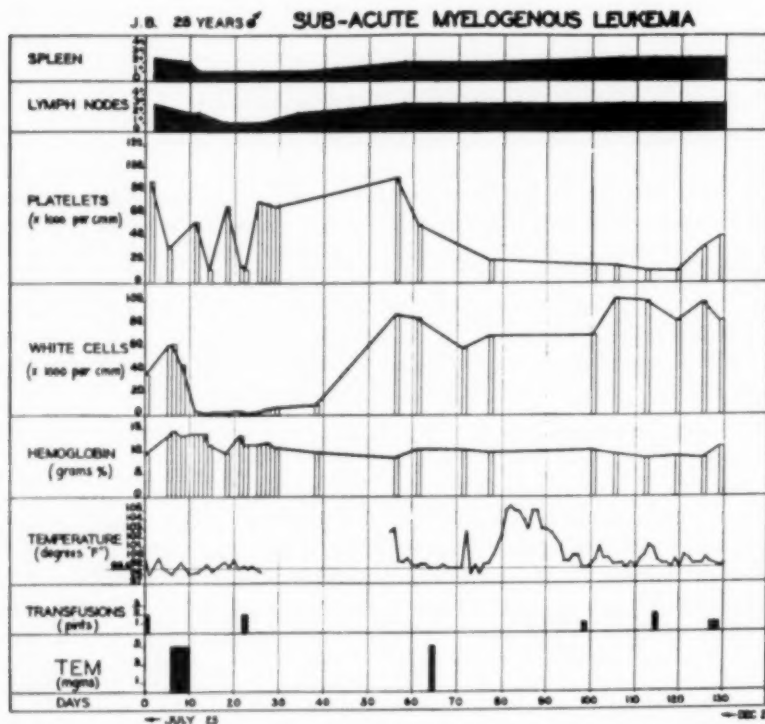


FIG. 5. Case 31. Subacute myelogenous (granulocytic) leukemia in an adult, showing response of leukocytosis, increase in thrombocytopenia and course after oral treatment with TEM.

normoblasts present. In the bone marrow smears, 62 per cent of the nucleated cells were myeloblasts, and a number of these blast cells showed Auer bodies. The blood urea nitrogen was 19.4 mg. per cent; uric acid, 4.4 mg. per cent; cephalin flocculation, 3 plus in 48 hours; bromsulfalein, 5.5 per cent retention in 45 minutes; thymol turbidity, 13 units; prothrombin time, 83.3 per cent of normal; serum bilirubin, 0.45 mg. per cent; cholesterol, 127 mg. per cent; cholesterol esters, 68 mg. per cent; alkaline phosphatase, 3.5 b.u.

Following the administration of 5 mg. a day of TEM for five doses, a dramatically rapid reduction in size of the lymph nodes and spleen occurred. This was accom-

panied by noteworthy general clinical improvement. However, following this initial course the white cell count fell to as low as 1,800 per cubic millimeter, and leukopenia persisted for one month. Further reduction of an already decreased platelet count also occurred, with temporary recovery to former levels after three weeks but with persistent severe thrombocytopenia later in the patient's course. By August 25, 1950, he had improved sufficiently to permit a short visit at home. However, he was again admitted on September 17, 1950, because of further enlargement of the hematoma of the left thigh. After a prolonged downward course, during which fresh whole blood transfusions and antibiotics were used without improvement of the hematoma, the leukemia gradually became acute and the patient died on February 25, 1951. Autopsy showed leukemic infiltration into the lungs, myocardium, aorta, gastrointestinal tract, liver, spleen, pancreas, adrenals, kidneys and bladder. Ecchymoses, however, were not conspicuous, and there was no hemorrhage into the adrenals.

Comment: This report of a case of subacute granulocytic leukemia illustrates the initial sensitivity of the spleen and lymph nodes to TEM in this stage of the disease; lists the observable beneficial clinical effects, which last for only a few weeks, and calls attention to the obvious hazard of possibly adding to an existing thrombocytopenia when even small doses of TEM are given in this subacute stage of the disease.

MISCELLANEOUS NEOPLASMS

Five patients with tumors not originating in the reticuloendothelial or hematopoietic systems were treated with TEM (table 1). No worthwhile palliation was observed, save for one case of bronchogenic carcinoma of the lung with vertebral metastases who experienced relief of thoracic nerve root pain for four weeks.

DISCUSSION AND SUMMARY

A clinical comparison of the familiar intravenous nitrogen mustard (HN_2) and the new oral triethylene melamine is shown in table 3. It is thought that such a comparison, brief as it is, may be timely and serve to highlight some of the similarities and differences which exist in the action of these two chemotherapeutic agents. As shown in this table, among the advantages of oral triethylene melamine over the intravenous nitrogen mustard compound are its oral administration, which avoids the occasional venous thromboses encountered with HN_2 , and its obviation of the vomiting so frequently seen with the older compound. Hospitalization of the patient may often be averted, since it is well suited to the ambulatory case. Because TEM is easy to administer and has a relatively prolonged effect, it is well adapted to maintenance therapy. The new drug has an action qualitatively similar to HN_2 in Hodgkin's disease and lymphosarcoma, but also extends its therapeutic spectrum to include chronic lymphocytic leukemia. Careful control of the dose of TEM and appropriate follow-up studies are necessary to avoid serious bone marrow depression.

As shown in table 1, our best results with triethylene melamine were obtained in Hodgkin's disease. Effectiveness of the drug varied from pa-

tient to patient, but in general it could be correlated with the stage of advancement of the disease, its natural aggressiveness and the patient's general condition. As with the older intravenous HN_2 , oral triethylene melamine proved especially useful when the disease was generalized, in the early case with first toxic symptoms of fever and pruritus, and in some so-called x-ray-resistant cases. Since improvement following a course of TEM may frequently be incomplete, the compound is often appropriately combined with roentgen radiation to localized areas. However, such patients with localized disease might theoretically be benefited by a course of TEM when they are first diagnosed, although long-term studies with a large number of patients would be necessary to determine its efficacy in such cases.

Oral triethylene melamine appeared qualitatively similar to HN_2 in its general action against the lymphosarcoma group in a limited number of cases. Like HN_2 , TEM may be relatively ineffective against far advanced reticulum cell sarcoma, but may exert a favorable effect in moderately early cases of lymphocytic lymphosarcoma and follicular lymphosarcoma even when relatively small doses are used.

Our experience with oral triethylene melamine in leukemias has been limited (table 1). However, encouraging results were observed in several cases of chronic lymphocytic leukemia, as manifested by decrease of leukocytosis and improvement of splenomegaly and lymphadenopathy. One patient (case 23, figure 4) well illustrates the favorable effects obtained in chronic lymphocytic leukemia, and also indicates the potential susceptibility of this disease to bone marrow depression from TEM. It is our opinion that a patient with chronic lymphocytic leukemia should first be given a small test dose of TEM, and it is especially important that his blood count and platelet count be followed at regular intervals as long as small maintenance doses are being administered. In this disease TEM is considered an adjunct to time-tested x-ray therapy, with which it may at times be advantageously alternated in some patients.

In granulocytic leukemia a good effect was observed in one patient in a chronic stage, and good but temporary effect in another in a subacute stage. Although the limited number of patients precludes a general statement, it is our impression that the proper use of roentgen radiation, P_{32} and urethane probably offers optimal therapy for the average case of chronic granulocytic leukemia.

The key problem in TEM therapy is to deliver safely the required therapeutic dose while avoiding serious bone marrow depression. To accomplish this task requires careful follow-up observations after each dose, inasmuch as the correct total amount cannot be forecast. In general, in early cases of lymphoma the bone marrow depression that follows TEM therapy is usually temporary. However, in patients with far advanced disease and preëxisting marrow damage, serious, prolonged depression of marrow function may

ensue. Peak bone marrow depression occurred at 12 to 50 days or longer after beginning TEM therapy, and varied greatly among the patients of the series. Thrombocytopenia was late in making its appearance in some cases. Bone marrow studies in those patients developing leukopenia, thrombocytopenia and anemia showed hypoplasia of the nucleated cells, especially of the megakaryocytes, increased numbers of degenerating cells and some increased granulation of the granulocytic elements.

To avoid serious marrow depression, an initial test dose of 2.5 mg. or 5.0 mg. of TEM is suggested. The blood count and platelet count should be determined before subsequent doses are given, and TEM therapy should be suspended whenever and if indicated. Patients with chronic lymphocytic leukemia may be especially susceptible to marrow depression, hence careful dosage control is of the greatest importance in these cases. When marrow depression occurs despite precautions, blood transfusions and antibiotics are the most valuable supportive measures. Cortisone and ACTH were of only limited benefit in treating marrow depression due to TEM therapy in nine patients in the series.

Gastrointestinal upsets were not a serious toxic effect in our experience. Anorexia and nausea, however, were experienced by the majority of patients at some time during their course of treatment. These symptoms were apt to occur five to 12 hours after a dose of TEM, especially if several 5 mg. daily doses had already been given. Vomiting occurred in only two of the 38 patients and was easily controlled in each case. Uremia due to hyperuricemia¹⁰ as a complication of TEM therapy was not encountered in our patients.

CONCLUSIONS

1. Triethylene melamine (TEM), a nitrogen mustard-like compound, is an important addition to the armamentarium of chemotherapeutic agents used in the palliation of lymphoma and leukemia.

2. TEM is valuable in the treatment of Hodgkin's disease where its action appears qualitatively similar to that of the nitrogen mustard, HN₂. It is also useful in some cases of lymphosarcoma. Small doses may produce a favorable effect in chronic lymphocytic leukemia.

3. TEM is indicated when the disease is generalized, in the patient with toxic, constitutional symptoms, and in some so-called x-ray-resistant cases. It may also be used advantageously in conjunction with local x-ray therapy.

4. TEM possesses certain advantages over HN₂: its easy oral administration, the decreased incidence of nausea and vomiting, and its adaptability to sustained maintenance therapy.

5. Because of the prolonged, cumulative action of TEM, the variable dose required for therapeutic response, and the variable tolerance exhibited by individual patients, adequate precautions in its use are highly desirable.

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CLINICAL EXPERIENCE WITH SYMPATHETIC BLOCKING AGENTS IN PERIPHERAL VASCULAR DISEASE *

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DURING the last five years numerous agents capable of blocking the sympathetic nervous system have been utilized in the study and treatment of peripheral vascular disease.¹⁻⁸ Although these agents act in different ways and at different sites, the objective—a partial or complete blockade of the sympathetic nervous system—is the same. This "sympatholytic" effect may be produced by a substance which interferes with sympathetic vasoconstrictor reflexes through a central site of action,^{9, 10} or peripherally, by a drug which blocks sympathetic nerve activity at the neuroeffector junction^{11, 12} (figure 1). In addition to inhibiting the response to sympathetic nerve stimulation, an agent of this type may also have an "adrenolytic" effect by blocking or reversing the effects of injected epinephrine or norepinephrine. Drugs which produce both effects have been termed "adren-ergic blocking agents."¹³ A third site of action is at the ganglion itself. Here, however, both parasympathetic and sympathetic impulses are blocked.⁴

Among the most promising of the newer sympathetic blocking agents are: Priscoline, Dibenamine,¹⁴ the dihydroergot preparations, Etamon and, more recently, the methonium compounds, Hexamethonium and Penta-methonium, a Dibenamine derivative, Dibenzylamine (S. K. F. 688A),^{16, 18} and Apresoline (C-5968).^{17, 18} Other agents, such as Benzodioxane¹⁹ and Regitine,²⁰ have been utilized in recent years because of their "adrenolytic" properties, but these preparations lack a "sympatholytic" effect and consequently are of only limited value in clinical medicine. They are useful, however, in the study of conditions such as pheochromocytoma, where an excessive amount of circulating adrenalin is present.

During the past two years, patients with peripheral vascular disease and hypertension have been studied and treated by us with the drugs mentioned. Results obtained in hypertension have been presented elsewhere.²¹ The purpose of this report is to summarize our experience with intravenous and oral Dibenzylamine,† oral and parenteral Hexamethonium,‡ and oral and intraarterial Priscoline in various forms of vascular disease.

* Received for publication January 30, 1953.

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† Supplied by Smith, Kline and French Laboratories, Philadelphia, Pa.

‡ Supplied by E. R. Squibb Co., New York, N. Y.

Dibenamine and Derivatives: It has been demonstrated that intravenous Dibenamine (5 to 7 mg. per kg.) is a potent adrenergic blocking agent.^{14, 22} It is useful in the treatment of hypertensive crises²³ but is ineffective orally and cannot be given subcutaneously or intramuscularly because of its irritant qualities. Rapid intravenous administration may result in severe reactions.

Dibenzylamine (S.K.F. 688A) is a Dibenamine derivative which, when given intravenously, is approximately eight times as potent as the parent substance. It is orally effective in doses of 30 to 240 mg. daily. Its actions are specific and side effects are usually not too severe.

A continuous partial blockade of the sympathetic nervous system and a lowering of blood pressure in the upright position have been obtained with

SITE OF ACTION OF AUTONOMIC BLOCKING AGENTS

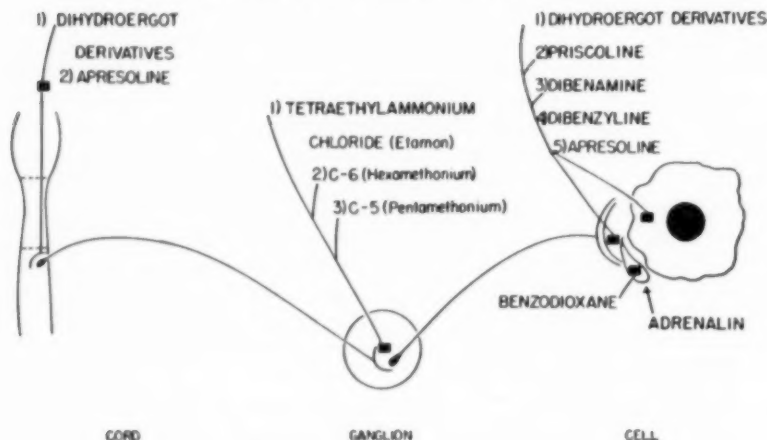


FIG. 1. Site of action of autonomic blocking agents.

Dibenzylamine^{18, 19} in hypertensive patients. A decrease in renal blood flow does not occur despite the fall in blood pressure.²⁴ Some observers have been unable to detect an alteration in peripheral blood flow following oral Dibenzylamine,²⁵ but others²⁶ have demonstrated an increase in foot blood flow following intravenous administration.

Methonium Compounds: Numerous studies have confirmed the observation that C-6 and C-5 (Hexamethonium and Pentamethonium) are potent ganglionic blocking agents.^{4, 9, 27}

It has been repeatedly demonstrated that 50 mg. of Hexamethonium (C-6) given intravenously increases skin temperature and blood flow as much as does a paravertebral block or a sympathectomy, and more than 500

mg. of intravenous Etamon or 50 to 75 mg. of intravenous or intraarterial Priscoline.^{28, 29} Studies carried out before and after sympathectomy have established the reliability of Hexamethonium in predicting the outcome of surgical procedures in most instances. Oral administration of this agent is not always satisfactory because of the variability in dosage.

Priscoline: Priscoline administered either parenterally (50 mg.) or orally (150 to 200 mg. per day) has a direct action on smooth muscle and is a fairly effective adrenergic blocking agent. Grimson et al.⁸ and Goodwin and Kaplan³¹ showed that Priscoline is orally effective and a satisfactory vasodilator, and is clinically useful especially in vasospastic conditions. Priscoline has been used intraarterially in an effort to produce a maximal effect in a limited area by "trapping" the drug.³²

MATERIALS AND METHODS

Eighty-four patients with various forms of vasospastic and occlusive vascular disease have been studied and treated with oral and parenteral Hexamethonium (C-6), parenteral Pentamethonium (C-5),* oral and intraarterial Priscoline, and oral and intravenous Dibenzyliline (S.K.F. 688A). Approximately one-half of the patients were hospitalized during the entire period of treatment. Twenty were started on therapy as hospital patients and continued as outpatients. The remaining patients were treated continuously as outpatients. Duration of treatment varied from one week to two years. Several of the patients have been observed for five to seven years by one of us (A. G. P.).

Skin temperature response was determined by use of the Leeds & Northrup Potentiometer. Venous occlusion plethysmography was employed to determine digital blood flow in many patients before they were placed on therapy and at intervals after treatment was started. This method has been described in detail elsewhere.²⁸ In addition, the skin temperature response to cold was studied in most patients before and after drug therapy. Observations were repeated on numerous occasions. All blood flow and skin temperature observations were made at constant temperatures in a room with a constant rate of air circulation and with the patient at rest and lightly clothed. Series of observations were made in a warm environment, 25° to 27.5° C. (77° to 82° F.), at usual room temperatures, 22° to 25° C. (71.5° to 77° F.), in cool environments, 19° to 22° C. (66° to 71.5° F.), and in cold environments, 10° to 19° C. (50° to 66° F.). In addition, blood pressure and pulse were recorded in both the recumbent and standing positions, and intravenous neosynephrine, the cold pressor test, and the Valsalva test and breath-holding maneuvers were employed at frequent intervals to determine the degree of sympathetic blockade.

* Supplied by Parke Davis Co., Detroit, Michigan.

RESULTS

Raynaud's Syndrome and Other Vasospastic Conditions: Thirteen patients with typical Raynaud's syndrome and 10 with definite evidence of sympathicotonia—hyperhidrosis, abnormal vasoconstrictor activity and acrocyanosis—were observed. One patient with Raynaud's phenomena and scleroderma, and one who had had a bilateral dorsal sympathectomy but had a return of symptoms, were also studied. In all patients, characteristic color changes were produced after exposure for from five to 20 minutes in a cold room before therapy was begun. Oral Priscoline, in doses of 100 to 200 mg. daily, or oral Dibenzyliline, in doses of 20 to 50 mg. three or four times a day, was then given. In most instances patients were placed on oral Dibenzyliline after a three to four week trial of Priscoline. Placebos were substituted for the drugs at frequent intervals. Any patient who responded to placebo medication was not included in the "results." Patients were seen daily while hospitalized and one to three times weekly as outpatients. Response to intravenous Hexamethonium or Pentamethonium was used as a standard for comparison to determine the degree of sympathetic blockade obtained with oral medication.

Effect of Priscoline: Initially, four of the 11 patients with typical Raynaud's syndrome noted some clinical improvement while on oral Priscoline. In spite of maintenance therapy, the degree of improvement decreased after several weeks. The remaining seven patients experienced no relief on Priscoline. In two cases, some reduction in the number of blanching attacks was obtained but a definite increase in perspiration occurred. Oral Priscoline was successful in alleviating symptoms of only four of eight patients with abnormal vasoconstriction.

Effect of Dibenzyliline: Ten of the 13 patients noted a definite decrease in the number, severity and duration of blanching attacks when first placed on oral Dibenzyliline. The relief obtained was significantly greater than after Priscoline. The following case illustrates the results obtained with this drug.

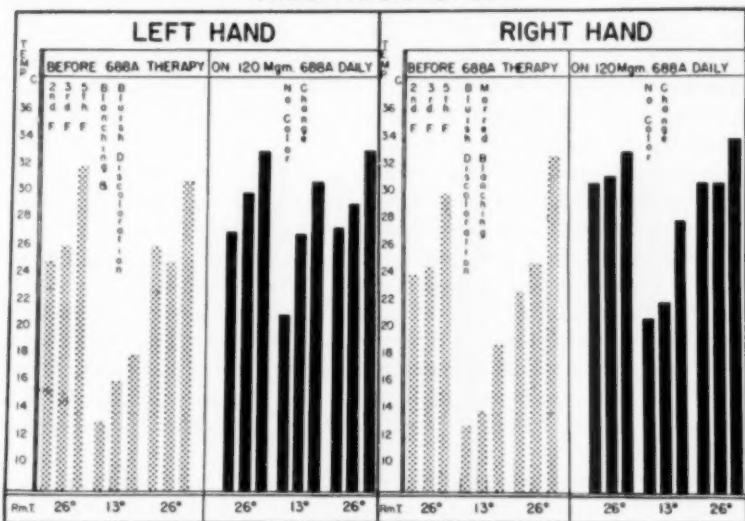
CASE REPORT

A 30 year old bombardier experienced episodes of painful blanching of the second and third fingers of both hands whenever he was exposed to cold, and especially on bombing missions, when he flew higher than 10,000 feet. Three months prior to his admission to Walter Reed Army Hospital, a skin biopsy specimen had been taken from the tip of his right second finger. Despite the fact that he was hospitalized and received continuous oral Priscoline therapy (200 mg. daily), episodes of blanching continued and the wound failed to heal. After two weeks of oral Dibenzyliline (20 to 60 mg. three times daily) wound healing occurred, the finger tip was no longer sensitive, and episodes of blanching became infrequent. A definite protection against cold was demonstrated (figure 2). The patient was sent home on leave and instructed to take 40 to 80 mg. of Dibenzyliline one and one-half to two hours before going out in cold weather. He was not kept on a definite dosage schedule. During a 30 day period the average temperature in his home town was 34 degrees. Only one severe

episode of blanching occurred, and only a few short, nonpainful attacks were experienced. The finger tip remained healed. After nine weeks of therapy the patient was given placebos. Two weeks later the number of attacks increased, although they were less severe than those which occurred prior to Dibenzylamine therapy. The right index finger again became cold and tender, and a small area of gangrene occurred under the nail. Treatment with Dibenzylamine again resulted in improvement. The drug was discontinued during warm weather and the patient instructed to begin therapy again with the onset of cold weather.

During the first few days of treatment the patient felt sleepy and "drunk." A "stuffy nose," postural tachycardia, hypotension and some dizziness on standing were experienced during the first two weeks of therapy. These symptoms gradually disap-

COLD ROOM STUDY



L.W. 30 yr M Raynaud's Syndrome

FIG. 2. Skin temperature responses at (a) room temperature of 26° C. (78.5° F.), (b) in cold room, 13° C., (55° F.) for 20 minutes, (c) after return to 26° C. (78.5° F.) environment for 20 minutes before and after 688A (Dibenzylamine) therapy.

peared. Pupillary constriction, a blockade of the usual cold pressor blood pressure response, and a transient fall in blood pressure following the intravenous administration of 1.0 mg. of neosynephrine were noted while the patient was on Dibenzylamine.

Although complete freedom from attacks was not obtained, both the frequency and the severity of attacks were reduced sufficiently to prevent further tissue damage and to enable the patient to lead a fairly normal life. It was felt that the use of intermittent administration of the drug prevented the occurrence of an "accommodation" or "adjustment" similar to that seen in several patients after continuous therapy over a two to 20 week period.

In two patients, side effects proved more troublesome than the original symptoms and the drug was discontinued. One patient obtained an excellent

response from placebos and was therefore given neither Priscoline nor Dibenzyliline.

Eight of the 12 patients with cold, clammy extremities but without actual Raynaud's phenomena obtained relief. There was a decrease in sweating, cyanosis and coldness of the extremities within two hours after Dibenzyliline therapy was begun. The effect was maintained for one and one-half to three hours, and symptoms were kept at a minimum in most cases by the administration of 20 to 50 mg. of Dibenzyliline four times daily. Therapy was started with 10 to 20 mg. four times a day, and gradually increased over a period of four to six days until a therapeutic response was obtained. In most instances, at least partial relief of symptoms was obtained on 30 mg. three times daily. In cases where "vasospasm" was delaying wound healing, and where patients were hospitalized and the danger of severe hypotensive reactions was minimized, more intensive therapy was instituted and other drugs in addition to Dibenzyliline were employed. For example, a 20 year old soldier, wounded in Korea, required a right mid thigh amputation. He was referred to the vascular clinic because the stump wounds had not healed despite two months of hospitalization and local therapy. The stump was cold and cyanotic and two separate open wounds, $3\frac{1}{2}$ by 2 inches, and 2 by $2\frac{1}{2}$ inches, were noted. Eighty milligrams of Dibenzyliline were given orally as a test dose, and within 90 minutes the stump was warm, dry and normal in color. The patient was then given 50 mg. of Bistrium Bromide (C-6) subcutaneously at bedtime, and 40 to 60 mg. of oral Dibenzyliline 20 minutes before meals. Although the patient became quite drowsy and complained of a severe stuffy nose and an occasional headache, therapy was continued, and after 20 days the wounds had completely healed. The stump remained warm and dry throughout the period of treatment.

In those instances where vasospastic phenomena were confined to one extremity and it was felt that therapy would have to be continued for long periods to achieve the desired result, surgical sympathectomy was usually advised. A 20 year old male, for example, had been frostbitten in Korea 14 months before being admitted to Walter Reed Army Hospital. He had noted healing of several lesions over the tips of the toes of his right foot, but a persistent ulceration of the heel area, excessive perspiration and intense coldness of the foot persisted. He was given 20 mg. of Dibenzyliline three times daily, with gradually increasing doses. By the end of one week he was receiving 60 mg. four times a day. The foot became warm and dry and the ulceration healed rapidly. Symptoms returned three weeks after therapy was stopped and the heel again became tender and opened. A right lumbar sympathectomy produced good results. One patient with evidence of sympathetic overactivity experienced feelings of "extreme fatigue" which continued for a longer time than in the other cases who were on Dibenzyliline, and the drug was discontinued. Another patient obtained little benefit from Dibenzyliline after the first four days of therapy, despite the fact that he had received

80 to 100 mg. four times daily and had initially obtained a dramatic response to 40 mg. of Dibenzylamine orally and 40 mg. of intravenous Pentamethonium (C-5). This patient probably represents a case of rapid "vascular adjustment" * in the presence of a sympathetic blockade.

Effect of Bistrium Bromide (C-6): Intravenous C-6 was given to four of the patients with Raynaud's phenomena and to six with acrocyanosis. In all instances, after a 50 mg. dose there was an immediate return of normal color and warmth. Sweating (as determined by the cobalt chloride method) was eliminated, and it was impossible to produce an attack of "vasospasm" after a 20 minute exposure to cold (13°C . [54°F .]) (figure 3). The most dramatic response occurred after the first dose. Parenteral C-6 was administered repeatedly to four patients in this group and proved to be a definite aid in cases of vasospasm with poor wound healing.

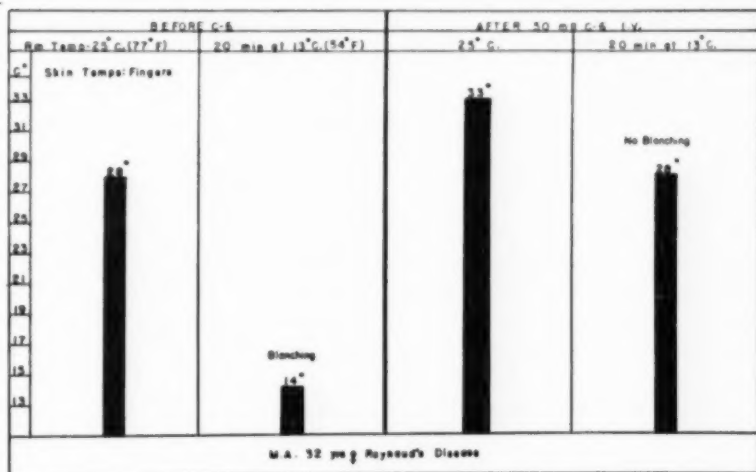


FIG. 3. Blockade of vasoconstrictor response to cold by C-6 (Hexamethonium).

Parenteral therapy with C-6 in outpatients was not considered feasible, since rest periods of at least one hour after each dose were necessary to avoid severe postural hypotension and syncope. Administration of oral Bistrium chloride (1 gm. one hour before exposure to cold) to two patients with Raynaud's disease was not satisfactory, since the time of onset of action of the drug could not be predicted. An excellent protection against cold stimuli was demonstrated, however, and there was a good clinical response in one patient who was maintained on 250 mg. of C-6 orally four times a day for a two week period. No significant side effects were seen in this normotensive individual.

* A return of vasomotor tone which is probably intrinsic and not under the control of the sympathetic nervous system.

OCCLUSIVE VASCULAR DISEASE

Twenty-eight patients with occlusive vascular disease were studied and treated. These included 10 cases of traumatic or postoperative arterial insufficiency, 10 of thromboangiitis obliterans, and eight of arteriosclerosis obliterans.

After initial skin temperature and/or blood flow studies, the ambulatory patients were treated with oral Priscoline or Dibenzyliline. Hospitalized patients were treated with parenteral C-6, intraarterial Priscoline and/or oral Dibenzyliline. Oscillometric and clinical response to standard exercise tests was determined before and after institution of therapy.

In this group of patients digital blood flow increases and/or skin temperature responses were more marked following intravenous C-6 (50 mg.) than after intraarterial Priscoline (50 mg.). Eighty to 150 mg. of oral Dibenzyliline and 1 mg. per kilogram of intravenous Dibenzyliline occasionally produced a dramatic result, but in some patients a rapid "vascular adjustment" occurred and there was no further effect after the first week of therapy, even though the dosage was increased. Some "adjustment" also occurred following repeated doses of oral or intraarterial Priscoline and intravenous or subcutaneous C-6.

A sympathectomy was done in any patient in whom a significant increase in blood flow and/or skin temperature was initially produced by any of the drugs, and in whom the disease was confined to one or at most two extremities, since it was determined that maintenance drug therapy was not practical and would not be permanently effective.

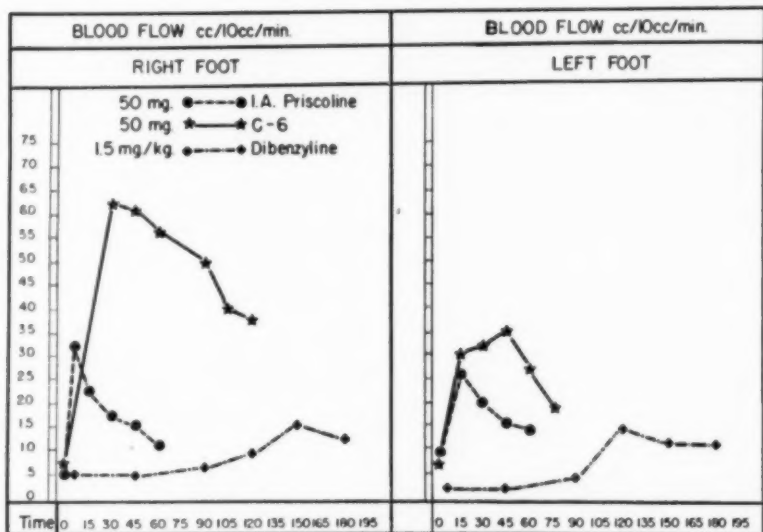
In two of the patients treated in this manner, the digital blood flow and skin temperature response to sympathectomy was good but symptoms were not alleviated. There was, therefore, no absolute correlation between digital blood flow increase and clinical improvement in these cases.

In 20 of the 28 cases actual organic vessel narrowing in the affected extremities precluded a significant increase in blood flow following drug administration, even though a release of vasoconstrictor tone had been achieved in the unaffected areas. In these cases sympathectomy was not advised and the patient was managed conservatively.

For example, a 30 year old male with thromboangiitis obliterans confined to the left leg was referred for studies prior to sympathectomy. Blood flow response to intravenous C-6, intraarterial Priscoline given into the left femoral artery and oral Dibenzyliline revealed that only a slight increase in flow was produced on the left when compared with the increase on the right (figure 4). The greatest increase in blood flow was produced by C-6. Oral Dibenzyliline was not effective in this case. On the basis of previous experience with C-6 and its use in predicting the effects of sympathectomy, surgery was not recommended. The degree of organic involvement, plus the finding of only a relatively small "vasoconstrictor" component, indicated that

a sympathectomy would not have helped this patient. However, the patient stopped smoking and did very well without specific therapy.

In some instances, use of autonomic blocking agents prior to a contemplated sympathectomy may actually indicate that sympathectomy would produce adverse results. For example, a 67 year old man entered the hospital with a four month history of severe intermittent claudication and two weeks of continuous pain over the dorsum of his right foot. Peripheral pulsations were absent and there were gangrenous areas over the tips of the first and second toes. A definite increase in pain and a decrease in skin temperature



W.D. 30yr. Thromboangiitis Obliterans — Left Leg

FIG. 4. Blood flow response to oral Dibenzyline, intravenous C-6 and intraarterial Priscoline.

in the foot followed 50 mg. of intraarterial Priscoline and, later, 1 mg. per kilogram of intravenous Dibenzyline. It had been our experience that patients who showed this response to drugs usually demarcated rapidly following sympathectomy; consequently, surgery in this case was deferred.

While on oral Dibenzyline only one patient with arteriosclerosis obliterans and one with thromboangiitis obliterans showed sustained increases in exercise tolerance* which were significantly greater than with placebo medication. Prolonged administration of Priscoline produced a definite improvement in two patients with arteriosclerosis obliterans who were not improved on Dibenzyline.

* An increase of 50 per cent or more in the number of steps climbed or distance walked without pain for two or more weeks.

Despite repeated demonstrations that a fairly large "vasoconstrictor" element was present in one patient with arteriosclerosis obliterans, and that the vasoconstriction could be released by oral Dibenzyline or Priscoline, no significant increase in exercise tolerance was noted when the patient was maintained on these drugs.

In three patients with thromboangiitis obliterans in whom a definite sensitivity to cold was demonstrated, both oral Priscoline and oral Dibenzyline were effective in preventing the marked fall in skin temperature which

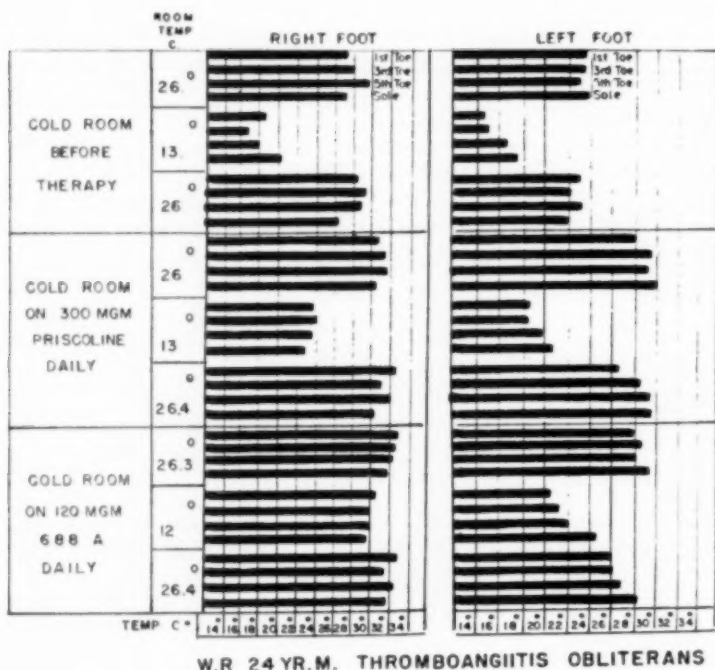


FIG. 5. Effect of oral Dibenzyline and Priscoline on skin temperature response to cold.

occurred when the patient was placed in a cold room for 20 minutes (figure 5). Dibenzyline was more effective and was used in these patients in much the same manner as in Raynaud's phenomena—40 to 80 mg. taken one and one-half to two hours prior to exposure to cold weather. In one patient in whom the episodes of vasoconstriction were confined to one foot a sympathectomy produced good results.

In general, side effects, such as "goose flesh," increased perspiration and occasional nausea while on Priscoline therapy, and transient dizziness, stuffy nose and fatigue while on Dibenzyline, were more marked in the patients

with arteriosclerosis obliterans. Consequently, the dose given was usually less than that for younger patients.

"Postfrostbite Syndrome": Seventeen patients who had experienced frostbite three weeks to four years prior to referral for treatment were given oral Priscoline (150 to 200 gm. per day for two weeks to two months), or oral Dibenzyliline (80 to 160 mg. per day for from two to eight weeks). In addition, all patients received one or more injections of Hexamethonium or Pentamethonium intravenously.

The symptoms most frequently noted in this group were aching of the affected extremity, increased sweating, occasional burning or "pins and needles" sensations, and increased susceptibility to cold. The involved foot or hand was usually cold to touch. Hyperhidrosis, often with a foul odor, was noted in most cases. There was some acrocyanosis in 12 patients, and all showed an abnormal vasoconstrictor response to cold. Fifteen patients also showed hyperhidrosis and increased sensitivity to cold in the extremities which had not been frostbitten. In most instances, some evidence of sympathetic nervous system overactivity had been present long before the cold injury occurred. In eight patients, one or more toes or fingers had been amputated because of gangrene.

Intravenous C-6 or C-5 produced warm, dry extremities in all patients, but only three experienced even temporary relief from the "achy" feeling in the affected limb. The warmth, lack of sweating and lack of vasoconstriction in response to cold lasted two to four hours after the injection.

Oral Priscoline produced an increase in skin temperature and moderate protection against cold in seven patients, but hyperhidrosis persisted or was increased by therapy. Only one patient reported relief of "aching" and paresthesias.

Fifteen of the 17 patients noted a definite decrease in sweating (confirmed by the cobalt chloride method in seven) while on Dibenzyliline therapy. In three of these, severe fungus infections which had existed for many months and had not responded to treatment cleared rapidly. An increase in skin temperature, and a partial inhibition of vasoconstriction following exposure to cold, were also noted in 15 patients. In 11 of these the initial effect on skin temperature and sweating gradually lessened over a period of two to eight weeks, even though the dose of Dibenzyliline was increased. Only three patients experienced a significant reduction in symptoms. In the remainder the "aching" and paresthesias persisted.

In three patients whose persistent bilateral toe ulcerations had not healed after several months of bed-rest and Priscoline therapy, Dibenzyliline produced good results. Sympathectomies had been suggested for these patients. One of them has been cited under "Vasospastic Phenomena." The other two were placed on oral Dibenzyliline, 20 to 50 mg. four times daily. One was maintained on therapy for 12 days and the other was kept on medication for three weeks. Healing of the ulcerations occurred in both cases. Sym-

pathectomy was not considered necessary, since satisfactory healing was maintained after cessation of therapy.

Causalgic States: Sixteen cases of major or minor causalgia were studied and treated with Hexamethonium and Pentamethonium, and Dibenzylamine. Priscoline was given to only three patients in this group and proved to be of no great value.

The criteria employed in making a diagnosis of causalgia were the persistence of burning pain following an injury and the presence of trophic skin changes and hypersensitivity in the affected extremity. Each patient was first treated for four days with placebos. One patient noticed a complete disappearance of pain and was consequently maintained on placebo medication. The others failed to respond to placebos and were started on oral Dibenzylamine, 10 to 40 mg. four times daily. Four obtained little or no relief from therapy. Eleven noted a cessation of pain within one and one-half hours of beginning therapy, with a return of burning pain just prior to taking the next dose of the drug. After one week of Dibenzylamine, placebos were again substituted. Eight patients noted a return of pain, but three had no return of symptoms. They remained symptom-free for two weeks and were finally taken off placebo medication and returned to duty. One of these was a 19 year old soldier who had suffered a laceration of his left wrist in Korea eight months before admission. Immediately following the injury he noted the onset of burning pain, which persisted without relief in the fingers of his left hand. Physical examination revealed a suspicious, withdrawn male protecting his hypersensitive, cold and clammy hand. The skin was atrophic and "velvety" to touch. Four days of placebo therapy failed to relieve the patient's symptoms. Within eight hours after Dibenzylamine therapy was begun (patient had received two doses of 20 mg. each), the hand became warm and dry, and pain completely disappeared. After one week of Dibenzylamine therapy placebos were again substituted but symptoms did not return. After two weeks, all medication was stopped and the patient sent on leave. He returned one month later, symptom-free and with a completely changed personality. He was friendly and cheerful. After one more week of observation he was returned to duty.

The eight remaining patients who had a return of burning pain were given daily intravenous injections of C-6 or C-5 (50 mg.) for four days. Complete relief of pain was noted for from 30 minutes to two hours after each injection. None of these patients had permanent relief of pain after repeated blocks. In these cases sympathectomy was performed, with complete pain relief.

In the four patients who failed to respond to oral Dibenzylamine, one noted relief of pain following intravenous Hexamethonium. This patient had a sympathectomy with only partial pain relief. One of the remaining three patients was subjected to surgery, with poor results, while the others were managed on sedation and analgesics. One who had previously had a sympathectomy with poor results did not obtain relief with intravenous C-6.

"Phantom" Limb: One patient with severe pain and burning in a "phantom" limb obtained no relief from repeated intravenous injections of C-6 and oral Dibenzyliline.

Toxicity and Side Effects. Priscoline and Dibenzyliline: The toxicity and side effects of these drugs are listed in table 1. In only three instances was it necessary to stop the administration of Priscoline because of side effects. In two of these an increase in chest pain occurred and S-T depressions were noted after exercise. In the other patient there was a marked increase in perspiration. In most cases the effects tended to decrease after several weeks of administration of the drug.

Most of the adverse reactions to Dibenzyliline represented effects secondary to sympathetic blockade. In six patients the drug was discontinued because of these reactions. In eight others it would have been necessary to discontinue therapy if long-term administration had been considered

TABLE I
Side Effects of Priscoline and Dibenzyliline in Normotensive Patients

Priscoline	No.	Dibenzyliline	No.
1. Tightness of scalp	48	1. Dryness of mouth and stuffy nose	59
2. Goose flesh and chilliness	26	2. Drowsiness, weakness, fatigue	49
3. Nausea and/or vomiting	19	3. Dizziness and palpitations	37
4. Restlessness and/or irritability	6	4. Decrease in amount of seminal fluid	26
5. Palpitations	6	5. Nausea and vomiting	4
6. Increased sweating	3	6. Transient restlessness	2
7. Increase in precordial pain	2		
Total number of patients	78		82

necessary. These were patients with delayed wound healing or causalgic states where only temporary treatment was required. Large doses (120 mg. per day or more) were not administered to any patient over the age of 40, even for a short period of time. Usually, drowsiness, dizziness and palpitations partially disappeared after the patient had been maintained on therapy for several weeks. The stuffy nose generally persisted as long as the drug was effective. The decrease in seminal fluid continued throughout the course of drug administration. All patients were cautioned prior to institution of Dibenzyliline therapy about orthostatic hypotension and dizziness, but this was not a significant finding in the normotensive group.

One patient with primary pulmonary arteriosclerosis (not included in this study) died suddenly following 40 mg. of intravenous Dibenzyliline given over a five minute period. The patient was being treated with quinidine and had received .6 gm. approximately one and one-half hours prior to Dibenzyliline administration.

Hexamethonium and Pentamethonium: The major side effects of these drugs included dry mouth, loss of pupillary accommodation, marked postural

hypotension and dizziness. These symptoms lasted for one to three hours after the first dose of the drug. Patients were kept flat in bed for at least one hour after each of the first five to six injections. If a pronounced fall in blood pressure occurred, the foot of the bed was elevated. After several days of therapy patients usually became ambulatory 45 minutes to one hour after each injection without experiencing symptoms. In the patients with arteriosclerosis obliterans, dizziness and postural hypotension persisted for a longer time following each injection.

In this group of normotensive individuals we encountered no episodes of syncope or severe hypotension, as was noted in hypertensive individuals. No serious constipation, ileus or bladder difficulties were encountered.

DISCUSSION

Until the recent introduction of effective sympathetic blocking agents, only limited medical therapy was available to the patient with peripheral vascular disease. The older vasodilators, such as nicotinic acid, papaverine, Roniacol, alcohol^{33, 34, 35} and histamine,³⁶ did not consistently prevent constrictor responses to cold and emotional stimuli. These drugs were occasionally effective in abolishing vasoconstrictor tone. At best, however, they were temporary and in no way duplicated the effects of surgical blockade of the sympathetic system.

Until recent years, temporary or permanent surgical interruption of sympathetic impulses by block or resection remained the treatment of choice in many cases of delayed wound healing, vasospastic conditions and causalgic states. With the introduction of Etamon in 1946³⁷ it became possible to interrupt these pathways without resorting to surgery.

The major difficulty with chemical interruption of sympathetic pathways is the inability to achieve selective inhibition of one area of the body. Even though denervation of one limb is all that is required, the patient is subjected to a total blockade of the sympathetic system, with the attendant side effects. Another disadvantage of this type of therapy is the necessity for continuous medication.

The factor of tolerance further limits the usefulness of medical therapy. An "adjustment" or "accommodation" occurs in some patients who are treated for long periods. This "adjustment" to Hexamethonium can usually be overcome by increasing the dose, and may be delayed in the case of Dibenzylamine by employing interrupted rather than continuous therapy.

It would seem logical to reserve chemical sympathetic blockade for the treatment of patients with conditions involving two or more limbs, or those requiring only temporary or intermittent interruption of the sympathetic pathways to achieve a satisfactory result. Drugs might also be of value where a blockade of the sympathetic system is necessary to determine the degree of abnormal vasoconstriction as opposed to organic narrowing of vessels.

In certain cases where a condition has previously been treated surgically and there has been a return of vasomotor tone and symptoms, the continued use of oral medication may represent the only available therapy. In patients who have diseases involving both upper extremities, and in whom surgical denervation would be more extensive and less reliable than denervation of the lower limbs, medical therapy may also be a useful substitute.

It has been repeatedly demonstrated that Hexamethonium, the most potent of the newer agents, produces a maximal degree of vasodilatation when given intravenously (50 mg.) and otherwise simulates the results of surgical blocks or sympathectomy.^{28, 29} It would appear, therefore, that there is less need for surgical blocking procedures for diagnostic or temporary therapeutic purposes, except where the systemic effects of Hexamethonium might be undesirable, as in elderly patients or hypertensive individuals, where a severe hypotensive reaction might produce deleterious effects. In contrast to the difficulty often encountered in obtaining a satisfactory block by surgical means, intravenous injection will give definite results. Intraarterial Priscoline (50 mg.) and oral (80 to 160 mg.) or intravenous Dibenzyliline (1 mg. per kg.), given in an infusion over a 30 to 45 minute period, may also be used instead of stellate ganglion or paravertebral blocks, but occasionally a maximal release of vasomotor tone is not obtained with these agents. Once a blockade is achieved with intravenous Dibenzyliline, it may last for from 12 to 36 hours in contrast to the two to six hour effect noted after parenteral Priscoline or C-6 or surgical block.²⁹ The degree of release of vasomotor tone and protection against noxious stimuli produced by oral Priscoline and oral Dibenzyliline is not so great as after parenteral administration of these drugs. It is not nearly so complete as after parenteral C-6, but is adequate for most clinical conditions requiring long-term oral therapy. Hexamethonium is effective orally and is quite potent, but its action is unreliable because of irregular absorption.

Our studies have indicated that these drugs may be used effectively in the situations outlined. The use of the oral preparations for long-term administration, or in conditions where one extremity is involved and a definite indication for sympathectomy is present, such as unilateral abnormal vasoconstriction, does not appear to be justified in most instances. Occasionally, however, a continuous blockade of the sympathetic system for a short period will achieve the desired result and sympathectomy will not be necessary. This was noted in several of our patients with abnormal vasoconstriction and poor wound healing who were maintained on combined Hexamethonium and Dibenzyliline therapy for from one to three weeks.

Three of the 16 patients with causalgia did not require sympathectomies because of permanent elimination of pain after continuous chemical sympathetic block for one week. This permanent relief of the causalgic syndrome³⁰ has also been noted in patients after repeated surgical sympathetic blocks,³¹ and will probably occur in a large enough group of patients treated

chemically for short periods to justify delaying surgery until after a trial on a sympathetic blocking drug. A surgical sympathectomy can always be done in these cases if permanent pain relief is not obtained. Drug therapy was also helpful in producing relief in patients with causalgia who were awaiting surgery and who were participating in an active physical therapy program. In these instances even a temporary alleviation of symptoms enabled them to use the extremity and regain function more rapidly.

Oral Dibenzylamine proved to be a more potent agent than Priscoline in "vasospastic" conditions and causalgic states, but only occasionally was it superior to the latter drug in thromboangiitis obliterans and arteriosclerosis obliterans. It was our impression that only the patients with these latter entities who manifested a significant vasoconstrictor response to cold stimuli responded to either of these drugs or to sympathectomy. In many instances, the degree of organic vascular narrowing was severe enough to preclude a marked increase in blood flow following removal of sympathetic tone either medically or surgically. We feel that the use of these drugs in organic vascular disease should be reserved for acute conditions and for short-term treatment. In many patients, giving up the use of tobacco, keeping the body warm and limiting activity will produce as satisfactory results as will Priscoline or Dibenzylamine. Very occasionally a dramatic response to drug therapy will be noted, and for this reason a trial of medication should be given if possible.

The use of the drugs in patients with thromboangiitis obliterans is usually without danger. In the older group with arteriosclerosis, however, Priscoline and Dibenzylamine must be used with extreme care. Administration of Priscoline occasionally causes an occurrence of or increase in anginal pain and S-T depressions after exercise. In nine of the ten arteriosclerotic patients who received Dibenzylamine, a marked tachycardia occurred which certainly would have produced deleterious effects if therapy had been continued for any length of time. Some degree of postural hypotension also was noted, and dizziness was marked in three patients. Extreme caution should be used in giving this drug to elderly individuals. Small doses should always be employed (30 to 80 mg. per day).

Parenteral Hexamethonium produced severe postural hypotension in these patients for periods of from one to three hours after administration. This drug should not be used unless facilities are available for keeping the patient flat in bed for several hours. Elevation of the foot of the bed should be carried out immediately if a fall in blood pressure is noted. In a patient with arteriosclerosis obliterans and hypertension, extremely small doses (5 to 25 mg.) should be given first to determine sensitivity to the drug. Blood pressure falls are often precipitous in this latter group of patients. We have found that the use of intraarterial Priscoline, given in a period of three to four minutes at a rate of 15 mg. per minute, is usually much safer, especially in patients who are not hospitalized. This drug produces an acute effect on blood flow which, although less marked than with C-6, is sufficient to produce

satisfactory clinical results. Intravenous Dibenzylamine will also produce adequate release of vasomotor tone, but postural effects are as pronounced as after C-6, and more prolonged. The use of intraarterial Dibenzylamine is now under investigation.

In the group of patients with "vasospastic" conditions involving two or more extremities, our results have been good. Because of the seasonal climatic variation in severity of the disease, long-term *intermittent* therapy produces satisfactory results. Tolerance to drug effect is apparently delayed by this method of administration, and side reactions are generally not too severe in younger normotensive individuals. Only an occasional patient will have to stop therapy because of side effects. Protection against vasoconstriction secondary to cold was repeatedly demonstrated, and there was clinical improvement in a fairly high percentage of patients. Oral Dibenzylamine would appear to have a place in the treatment of these conditions.

It must be realized that a complete disappearance of symptoms and complete freedom from attacks cannot be achieved on any therapy presently available. Studies utilizing the cold room have demonstrated that even following surgical sympathectomy a gradual return of vasoconstrictor tone and "vasospastic" phenomena is noted.^{39, 40} The attacks, however, are of shorter duration and not nearly so severe as prior to operation.³⁹ Following drug therapy, definite diminution of vasoconstrictor responses to cold stimuli, as well as an almost continuous warming of the involved extremity, was noted. This was by no means complete, nor did we expect to achieve complete relief. Clinically, these patients were much improved. Fingertip or toe ulcerations healed quickly and the patients were able to lead fairly normal lives.

SUMMARY

1. The results obtained with oral and parenteral Dibenzylamine, oral and parenteral C-6, and oral and intraarterial Priscoline in a group of 84 patients with various forms of peripheral vascular disease are reviewed.
2. Dibenzylamine and Hexamethonium proved to be of value in the treatment of vasospastic conditions and delayed wound healing. They were found to be useful agents for producing release of vasomotor tone and increases in blood flow for *short* periods of time, and were useful as substitutes for surgical blocking procedures.
3. Results of therapy with Dibenzylamine in Raynaud's disease were good, but therapy with Priscoline or Dibenzylamine in organic vascular disease was usually not successful.
4. Dibenzylamine and Hexamethonium uniformly relieved causalgic pain. In three of 16 cases, pain did not return after cessation of drug therapy. It is possible that these drugs may prove useful in differentiating true causalgia from neuropathies.
5. Priscoline, Dibenzylamine and Hexamethonium were of little value in relieving the symptoms resulting from previous cold injuries (postfrostbite

syndrome), despite the fact that increases in skin temperature and/or blood flow, and a protection against vasoconstriction secondary to cold, were demonstrated in many instances.

6. Continuous long-term therapy with these agents does not appear to be feasible because of the development of a "vascular adjustment," but intermittent therapy appears to be beneficial in some patients. Since selective blockade of one portion of the sympathetic system cannot be achieved with these drugs, their administration on a long term basis should be limited to patients with disease involving more than one extremity. Surgical sympathectomy should remain the treatment of choice in instances where disease is limited to one area, but only where studies of vasomotor reactions indicate that sympathetic denervation would be helpful.

7. Dibenzylamine and Hexamethonium appear to be potent and useful agents in the study and treatment of vascular disease, although side effects may very definitely limit their use. They appear to be more effective than oral or intraarterial Priscoline, although in some instances intraarterial administration of the latter drug is to be preferred because of its "local effects."

ACKNOWLEDGMENT

The authors wish to thank Miss Ann Berman for technical assistance.

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THE EFFECT OF THE L. E. CELL TEST ON THE CLINICAL PICTURE OF SYSTEMIC LUPUS ERYTHEMATOSUS*

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FIVE years have passed since Hargraves described the L. E. (lupus erythematosus) cell,¹ and during that period there has been a profound change in the concept of systemic lupus erythematosus. It is the purpose of this paper to point out the pleomorphism of this relatively common disease, which occurs with one-half the incidence of acute rheumatic fever at the Los Angeles County General Hospital. There is no classic pattern of this illness, and the diagnosis must be based on an over-all view of the entire clinical picture with the aid of the L. E. test.^{2,3} Because of its varied forms, many of these cases are at present masquerading under other diagnoses.

The data to be presented were derived from a two and one-half year study of 62 new cases at this 3,600-bed hospital. Fifty-three of the patients were personally seen and examined by the author. Thirty-seven of them were specifically questioned about the symptoms, which will be discussed, utilizing a tabulating form listing the changes shown in tables 2, 3, 4, and 5.

INCIDENCE

The disease was diagnosed in only 11 cases from 1948 through 1949. During the following two calendar years, when we were actively seeking new patients and utilizing the L. E. test, the diagnosis was made in 44 cases. We do not believe that the general incidence is increasing, but rather that our diagnostic acumen is better and the concept of the disease broader. With the aid of Hargraves' test, which we feel to be pathognomonic, it is usually possible to confirm our tentative opinion. During the same 1950-1951 period there were 18 cases of Hodgkin's disease at this institution, 38 cases of all types of acute and subacute leukemia, and 36 cases of pernicious anemia in relapse, ailments which are not considered to be rare (table 1). During that same period 88 individuals with acute rheumatic fever were admitted. The incidence of lupus was exactly one-half that of rheumatic fever!

Our patients ranged in age from two to 67 years. All colors and races were seen, in a distribution similar to that of the hospital population; 88.7

* Received for publication December 17, 1952.

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Dr. Elmer K. Alpert, of Merck & Co., was kind enough to supply cortisone and compound F for this study. The Ciba Pharmaceutical Company supported this work in part.

Dr. I. C. Winter, of G. D. Searle & Co., also supplied additional amounts of compound F. Mr. Joseph H. Gluckstein of Los Angeles, Calif. aided this study by a generous financial grant.

TABLE I

Incidence of Systemic Lupus Erythematosus Compared to Some Other Disease Entities at the 3,600-Bed Los Angeles County General Hospital

1950-1951	Individual Cases Admitted
Systemic lupus erythematosus	44
Acute rheumatic fever	88
Acute and subacute leukemias (all types)	38
Pernicious anemia (new cases)	36
Hodgkin's disease	18
Periarthritis nodosa	13
Dermatomyositis	5
Scleroderma	4
Thrombotic thrombocytopenia	3
1948-1949 (Prior to our interest in LE and use of the LE test)	
Systemic lupus erythematosus	11

per cent were female; the median age was 26.6 years, and the mean, 27.5 years.

PATHOLOGY

In 1828 Bielt first described the discoid form of lupus, and five years later Cazenave and Schedel more fully pictured the illness.⁴ Kaposi in 1872 noted that some cases of lupus were accompanied by severe constitutional symptoms and might be fatal.⁵ He also recognized the fact that the disease was more common in women than men.

Osler in 1895⁶ first emphasized the fundamental concept that the alterations occurring in the skin of these patients had their counterpart in the internal organs, and indeed he described the occurrence of visceral lesions without skin changes, a concept only recently accepted. His succinct description of the illness is worth repeating: "By exudative erythema is understood a disease of unknown etiology with polymorphic skin lesions, hyperemia, edema and hemorrhage—arthritis occasionally, and a variable number of visceral manifestations, of which the most important are gastro-

TABLE II

Compilation of the Clinical Data of 62 Cases of Systemic Lupus Erythematosus

Race*	Individuals	Per Cent
White	29	46.7
Mexican	18	29.0
Negro	12	19.3
Japanese	3	4.8
Specifically interviewed about the symptoms listed	37	59.0
Living at end of study	37	59.6
Autopsied	15	24.2
Median duration of disease in entire group	28.5 months	
Mean duration of disease in the entire group	45.1 months	
Incidence of spontaneous remission		
Over-all group	24	39.7
Specifically interviewed	16	43.3
Not interviewed	8	32.0
Multiple remissions (over-all group)	12	19.3

* Racial incidence is comparable to that of the hospital population.

intestinal crises,* endocarditis, pericarditis, acute nephritis and hemorrhage from mucous surfaces. Recurrence is a special feature of this disease and attacks may come on month after month or even throughout a long period of years. The attacks may not be characterized by skin manifestations; the visceral symptoms may be present and to the outward view, the patient may have no indications whatever of erythema exudativum." This pattern of the illness is still as correct as when it was written. The polymorphism of the disease such as Osler describes will be pointed out in this paper.

Libman and Sacks in 1924 described an atypical verrucous endocarditis occurring in cases of lupus erythematosus.⁷

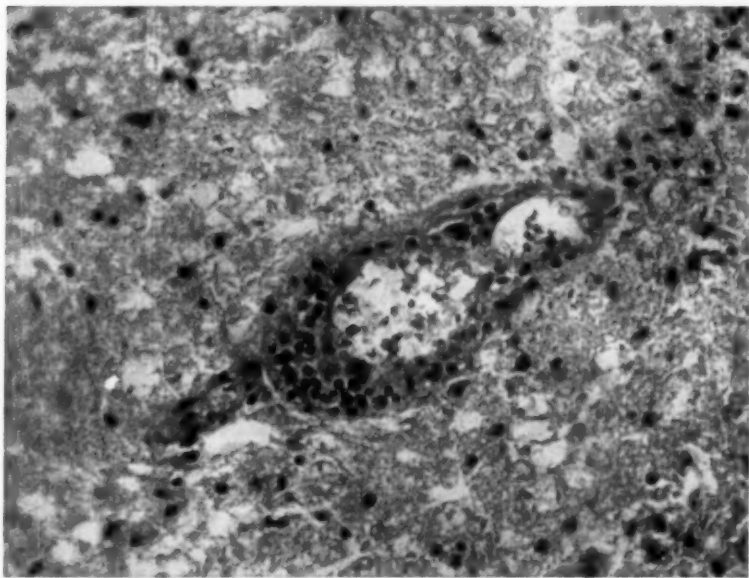


FIG. 1. Acute arteritis and edema of the surrounding tissue in the spinal cord of a 22 year old patient with a paraplegia due to lupus erythematosus. (750 X.)

In 1935, Baehr, Klemperer and Schifrin advanced the pathologic study by their description of certain well defined alterations in the blood vessels, especially in the kidney—the so-called "wire-loop" lesions of the glomerular capillaries.⁸ Jarcho in 1936 demonstrated the peculiar splenic vascular alteration, the "onion-skin" change of the collagen about the arterioles.⁹ Since then, unfortunately, interest has centered about the collagen changes rather than the vascular ones. The blood vessel lesions, which resemble a peri-

* Until now these were thought very unusual, but as more cases are diagnosed by finding typical L. E. cells and little else, the great frequency of these symptoms as an initial or later manifestation of lupus will be pointed out in this paper.

arteritis, with intimal swelling, occasionally thrombosis, periarterial polymorphonuclear and lymphocytic infiltrations and adventitial thickening, are very important in the causation of the central nervous system changes, and ocular, intestinal, skin and renal damage. In some cases they may be found in almost all the other organs. Because of the extensive vascular involvement, the clinical picture may superficially resemble periarteritis nodosa.²⁴ Figure 1 shows an arteriole in the spinal cord of a patient who had a paraplegia due to lupus. Figures 2 and 3 show periarteritis in the liver and adrenal, respectively. Some of these patients have polyneuritis, and these

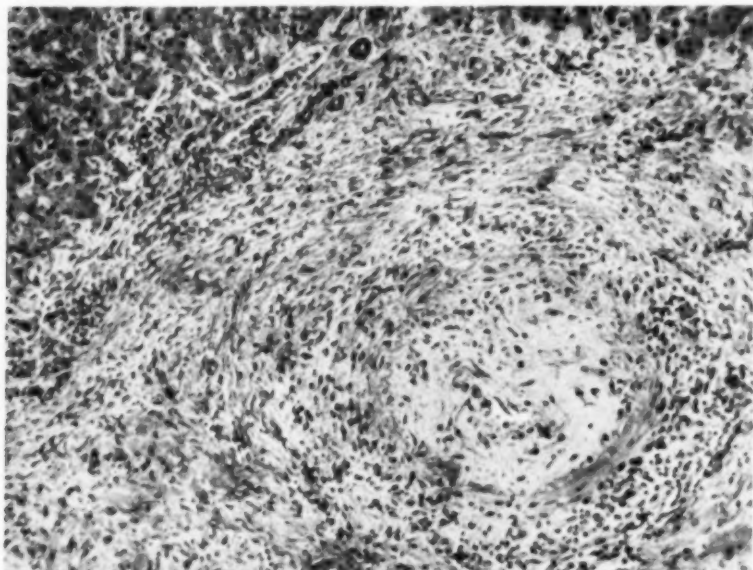


FIG. 2. Arteritis in the liver of a nine year old girl with classic systemic lupus erythematosus. There is almost complete obliteration of the lumen. (100 \times .)

changes are due to vascular involvement of the nutrient arteries of the nerves.¹⁰

Myositis is very common, and biopsy may show a picture compatible with a diagnosis of dermatomyositis.^{11, 17} (Figure 4.)

In 1940 Ginzler and Fox pointed out the "hematoxylin" bodies in the heart valves, lymph nodes and kidneys.¹² These bodies have subsequently been shown to be the same material as the inclusions in the L. E. cells.¹³ We have found them in the L. E. cell preparations. Their presence is highly suggestive of the disease, *but not diagnostic*, as similar changes may occur in scleroderma and in patients with hyperglobulinemia.

Malcolm Hargraves in 1948 described the peculiar inclusion bodies in the polymorphonuclear leukocytes which have been shown to be pathognomonic in our experience and that of others.^{1, 2, 14, 15, 16} This test has greatly expanded the breadth of our concept of lupus by enabling us to diagnose equivocal cases. It has also spurred the biochemical studies, which are the key to the etiology of the illness.

CLINICAL FEATURES

There is no classic pattern of this disease. As our knowledge of its varied manifestations is expanded, so the number of correctly diagnosed

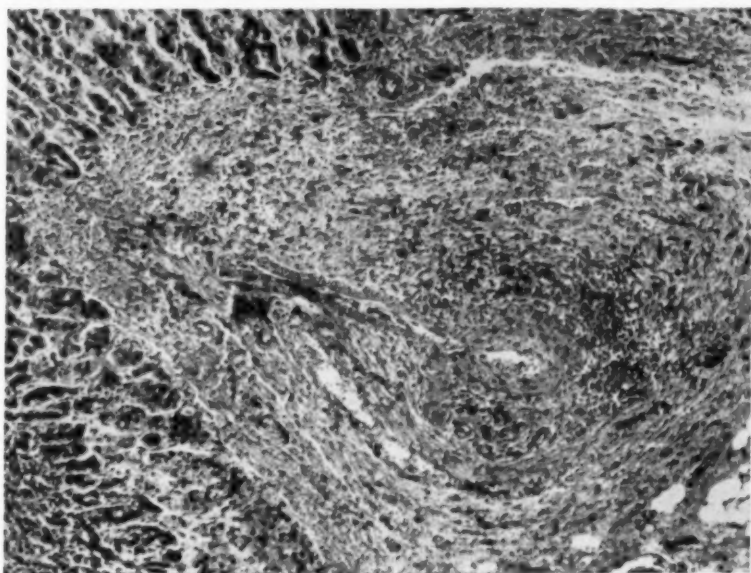


FIG. 3. Arteritis in the adrenal of a nine year old girl with classic systemic lupus erythematosus (the same case as in figure 2). (100 X.)

cases is increased. The illness is subject to many exacerbations and remissions, which may affect one system, such as the skin, and at the same time or years later affect another area, such as the kidney.^{2, 3, 14} Prior to the introduction of the L. E. test many of these cases could not be diagnosed, because although the multiplicity of systems involved suggested a "collagen disease," there was no simple way definitely to confirm the diagnosis.

Table 2 shows the incidence of spontaneous remissions in the series before hormonal treatment. Also tabulated in 3 and 4 are the patients' chief



FIG. 4. Pectoral muscle biopsy from case 9. Note the infiltration of mononuclear and polymorphonuclear cells between the muscle fibers.

complaints on entering the hospital as well as the system which the disease historically first involved. Those findings which were significantly different in the interviewed and non-interviewed patients are listed separately in the table.

TABLE III

Chief Complaints on Admission at Which Systemic Lupus Was Diagnosed

Complaint	Number of Individuals	Per Cent
Arthritis	18	29.0
Eruption on the butterfly area	10	16.1
Eruptions on other parts of body	7	11.3
Shortness of breath	6	9.7
Fever	5	8.1
Abdominal pain	4	6.5
Pleurisy	3	4.8
Lethargy	2	3.2
Positive serologic test for syphilis	1	1.6
Discoid lupus	1	1.6
Raynaud's phenomenon	1	1.6
Pericarditis	1	1.6
Tarry stools	1	1.6
Vomiting	1	1.6
Sore throat	1	1.6
Anorexia	1	1.6
Swelling of ankles	1	1.6
Weight loss	1	1.6

Spontaneous remissions occurred in 24 of these patients (39.7 per cent) prior to any specific therapy. Multiple remissions occurred in 12 cases. The lengths of the remissions varied from several weeks to eight years. The appearance of spontaneous improvement is very common and one of the characteristic features of the disease. Ben-Asher has described a 23 year remission in systemic lupus erythematosus.³¹

Since the illness affects arteries and veins as well as connective tissue,¹⁷ its clinical features will be quite variable and many of them will resemble changes due to periarteritis, scleroderma, rheumatoid arthritis, rheumatic fever, and a multiplicity of skin diseases. L. E. should always be considered in the differential diagnosis of these conditions and routine studies for the pathognomonic cells performed on both blood and bone marrow

TABLE IV

First System Involved as Determined by History

(Data are essentially the same for both interviewed and non-interviewed groups)

First System	Number of Individuals	Per Cent
Arthritis	21	34.0
Butterfly area eruption	10	16.1
Eruptions on other parts of the body	7	11.3
Raynaud's phenomenon	5	8.1
Hemolytic anemia	4	6.5
Pleurisy	3	4.8
Positive serologic test for syphilis	2	3.2
Discoid lupus	2	3.2
Pericarditis	2	3.2
Pleural effusion	2	3.2
Fever	1	1.6
Weight loss	1	1.6
Renal involvement	1	1.6
Pulmonary	1	1.6
Gastrointestinal tract	1	1.6
Epilepsy	1	1.6

samples. Below is an outline of the systems which may be involved singly or in any combination.

OUTLINE OF THE CLINICAL PICTURE OF SYSTEMIC LUPUS ERYTHEMATOSUS

1. Signs of catabolism: fever, weight loss, emaciation.
2. Connective tissue lesions: rheumatoid arthritis, subcutaneous nodules, pericarditis, Libman-Sacks syndrome with myocarditis, pleurisy, polyserositis.
3. Vascular lesions: skin, central nervous system, ocular fundi, kidney, gastrointestinal tract, adenopathy, splenomegaly, Raynaud's phenomenon, hyperpigmentation.
4. Hematologic changes: leukopenia, anemia (usually hemolytic), thrombocytopenia, increased circulating anticoagulant, false-positive serologic test for syphilis, L. E. cells.

Each of these changes will be discussed briefly and short cases presented to illustrate how any system may be the initial one involved. Table 5 shows the incidence of these changes in this series.

The fever curve may be of any type. Occasionally shaking chills occur without bacteremia. With the onset of fever, anorexia, weight loss, malaise and myalgia are common. The myalgia may be so prominent that many of these cases are called dermatomyositis (figure 4). A muscle biopsy may be suggestive of primary muscle involvement or periarterial changes in a patient who has lupus erythematosus.^{11, 17} One should be aware, however, of the nonspecificity of these biopsies, and studies for L. E. cells should be done regardless of the findings on tissue section.

CONNECTIVE TISSUE LESIONS

Arthritis is the most common presenting symptom of these cases and was found initially in 34 per cent of the cases. The picture is usually typical of early rheumatoid involvement. In most of the acute cases there is primarily arthralgia of the proximal interphalangeal joints, as well as of the elbows, knees and ankles. Acute fusiform-type inflammatory changes of the proximal interphalangeal joints are common in the exacerbations of the disease, and a persistent deformity occurred in 30.6 per cent of the cases. As far as one can tell, both clinically and pathologically the arthritis is indistinguishable from the idiopathic type of rheumatoid involvement. Many patients complain of joint involvement for many years prior to evidence that other systems are affected. They have multiple exacerbations and remissions. The following brief case report demonstrates this point.

CASE REPORTS

Case 1. M. S., an 11 year old white female, had complained of intermittent joint aching from the age of three years.

Shortly after her birth it was noted that the patient was running bouts of unexplained low grade fever. At the age of three she developed intermittent arthralgia in the knees. When she was five, pains appeared in her hands and in the major joints. She was studied by many physicians, but no definite diagnosis was made. There were many intervals of several months of freedom from arthritis. When she was eight and a half a false-positive Kahn and albuminuria were noted. The positive serologic tests for syphilis have persisted. When she was ten and a half, pink spots appeared about the cheeks. In the course of the next two months, after a great deal of exposure to the sun, she developed a typical butterfly eruption. At this time there was fever up to 104° F., as well as an exacerbation of her joint pains without rheumatoid deformity. She was hospitalized, and L. E. cells, hemolytic anemia, leukopenia and nephropathy were found. The disease responded dramatically to hormonal therapy.

Comment: This 11 year old girl had intermittent arthralgia for five and one-half years, followed by the appearance of positive serologic tests for syphilis. Two years later she developed the classic skin, hematologic and other changes of systemic lupus.

TABLE V

Incidence of Changes Due to the Disease

(Data are essentially the same for both the interviewed and non-interviewed groups unless specified.)

	Number of Individuals	Per Cent
Signs of Catabolism		
1. Fever	60	97.0
2. Weight loss	51	82.0
Connective Tissue Lesions		
1. Arthritis	56	90.0
a. Definite rheumatoid deformity	19	30.6
2. Pericarditis	27	43.5
3. Myocarditis	11	17.7
a. Heart murmurs (systolic)	26	42.0
4. Pleurisy	37	59.5
5. Pleural effusion	34	55.0
6. Ascites	15	24.2
Vascular Lesions		
1. Skin		
a. Skin lesions of all types (total)	52	84.0
b. Butterfly area lesions (both classic and atypical)	43	69.4
c. Photosensitivity of rash	25	40.3
d. Hyperpigmentation	10	16.1
e. Mucous membrane lesions	7	11.2
f. Loss of hair—over-all group	32	51.5
interviewed group (37)	26	70.0
non-interviewed group (25)	6	24.0
2. Central Nervous System		
a. Convulsions due to lupus	19	30.6
b. Convulsions due to therapy	3	4.8
c. Psychosis	15	29.0
d. Chronic nervous system damage	11	17.7
3. Fundic lesions	20	32.3
4. Kidney		
a. Urinary abnormalities	35	56.5
5. Gastrointestinal tract		
a. Nausea	22	35.5
b. Vomiting	25	40.3
c. Diarrhea	12	21.0
d. Abdominal pain	23	37.2
6. Adenopathy	26	42.0
7. Splenomegaly	5	8.1
8. Hepatomegaly	21	34.0
9. Raynaud's phenomenon—over-all group	16	25.8
interviewed group (37)	13	35.0
non-interviewed group (25)	3	12.0
Hematologic Changes		
1. Leukopenia (one count below 4,500)	42	68.0
2. Anemia (below 11 gm.)	48	77.5
3. Thrombocytopenia (marked)	6	9.7
4. Positive serologic test for syphilis	19	32.6
5. L.E. cells (performed in 60 cases—see text)	41	69.3
6. Hyperglobulinemia (over 3.8 gm. % at this lab—proteins done in 56 cases)	15	27.8
7. Positive L.E. test with hyperglobulinemia (15 cases)	13	86.5
Other Changes		
1. Electrocardiographic changes (marked)	23	37.0
2. Jaundice	7	11.3
3. Skin biopsy positive (performed in 23 cases)	12	52.3
4. Pleocytosis	4	6.4

Subcutaneous nodules as large as 2 cm. in diameter which are exceedingly tender occasionally may occur, especially on the extensor tendons of the hand and wrist. These lesions are often evanescent, and biopsy shows typical rheumatoid nodules.

Evidence of pericarditis was found by history in 43.5 per cent of the cases. The clinical picture is typical, with a complaint of substernal or precordial pain, aggravated by motion such as breathing, coughing, swallowing, twisting and bending forward. Symptoms may last from hours to weeks. In only a few of the cases does one hear the typical friction rub, but in 80 per cent of the autopsies evidence of pericarditis was found. The electrocardiogram may be confirmatory in the active phases. At times this is the first system involved, as in two of our cases. The following case history illustrates this pattern of systemic lupus.

Case 2. N. G., a 31 year old colored woman, was admitted to the Los Angeles County General Hospital in April, 1947, complaining of chest pain of five days' duration.

She had been in good health until April, 1946, when increasing fatigability appeared. During the summer of 1946 she experienced a four day episode of severe, drawing, pleuritic-type substernal pain with dyspnea. In March, 1947, the patient delivered a normal child and three weeks later had a recurrence of the same type of pain which she had had the previous summer, again without any preceding respiratory infection. This pain and dyspnea persisted for five days prior to hospitalization.

Physical examination revealed a well developed and well nourished 31 year old Negro female who was acutely ill with pleuritic substernal pain. Temperature was 101.8° F.; pulse, 140; respirations, 40; blood pressure 140/84 mm. of Hg. Her respirations were shallow and accompanied by an expiratory grunt. Other significant findings were decreased breath sounds at the right lower lobe posteriorly, with dullness in that area. The apex impulse was at the midclavicular line in the fifth intercostal space, and the left border of dullness was 1 cm. lateral to it. The heart tones were loud and regular, with a to-and-fro friction rub at the left sternal border which lasted 10 days.

The chest x-ray on admission showed hilar accentuation. There was no evidence of pleural effusion. The heart was water-bottle shaped and enlarged. Fluoroscopic examination several days later was suggestive of pericardial effusion. The electrocardiogram revealed the classic changes of acute pericarditis. Her hemoglobin was 10 gm. and the white cell count 13,400, with 84 per cent polymorphonuclear leukocytes. Urinalysis was normal.

The patient was treated with penicillin and sulfadiazine. Gradually during the course of the next three weeks she became afebrile. Ten days after admission, 60 c.c. of cloudy pleural fluid were removed from the right base. After leaving the hospital in 1947 she continued to be readily fatigued and occasionally febrile. At about this time Raynaud's phenomenon appeared and persisted. Dyspnea on mild exertion continued, and in December, 1951, she again returned to the hospital complaining of ankle edema and pleurisy of two weeks' duration. She had lost 20 pounds since her previous admission. Physical examination now revealed a chronically ill 35 year old colored woman with a temperature of 101° F. There was evidence of much recent weight loss. Mild generalized adenopathy was present. The heart was enlarged, with the apex beat at the fifth intercostal space at the anterior axillary line. There were no murmurs. Posteriorly there were bilateral dullness and diminished breath sounds. One plus ankle edema was present.

Urinalysis was normal. White blood count was 2,700, with a relatively normal differential. Hemoglobin was 9.0 gm., and the red cells were normocytic on smear. Albumin, 3.6, and globulin, 6.9, on several tests. The peripheral blood and bone marrow L. E. tests were positive. She responded well to hormonal therapy. Several months after treatment was instituted a false-positive serologic test for syphilis appeared. It reverted to negative again during the next few months of steroid treatment.

Comment: This 35 year old Negro female developed, as the first sign of systemic lupus acute pericarditis which spontaneously cleared. During the next four years she was chronically ill, and finally pleurisy appeared with leukopenia, anemia and hyperglobulinemia. The finding of L. E. cells confirmed the basic diagnosis. There have never been any skin changes or urinary abnormalities.

The following case illustrates how closely lupus erythematosus may mimic tuberculous or rheumatic pericarditis. In this case, too, there have never been any skin lesions.

Case 3. G. H., a 16 year old colored girl, was admitted to the hospital in August, 1951, complaining of painful hot joints of one year's duration. The patient had been in good health until one year prior to admission, when she developed migratory polyarthrits involving the knees, ankles and proximal interphalangeal joints. She was treated elsewhere with gold injections and pyrogens, with some improvement. During the two months before admission, increased joint pain and fever appeared.

Physical examination revealed a poorly nourished, and well developed 16 year old girl who was acutely ill. Temperature was 101° F.; pulse, 100; respirations, 20; blood pressure, 108/70 mm. of Hg. The significant finding was a grade 1 soft blowing systolic murmur in the mitral area. The heart was normal in size. All the joints of both extremities were hot, stiff and tender on motion. There were no skin, mucous membrane or eyeground abnormalities. Laboratory studies revealed a white cell count of 5,400, with a normal differential. Hemoglobin, 8 gm. per cent; sedimentation rate, 40 mm. per hour (Wintrobe); urinalysis, normal, sickle cell preparation, negative; antistreptolysin titer, 166 Todd units (a significant level).

After several febrile weeks in the hospital she began to complain of severe right upper quadrant pain, with vomiting and local tenderness for which no explanation was evident. X-rays of her joints showed significant changes only in the hands and wrists, with periarticular bony demineralization and fusiform swelling of the proximal interphalangeal joints of the fingers. One month after admission the patient began to complain of substernal pleuritic pains. Repeat x-rays of the chest and fluoroscopic study demonstrated a massive pericardial effusion and small bilateral pleural effusions. Forty cubic centimeters of serosanguineous fluid were withdrawn from the pericardial sac. Studies for tubercle bacilli and routine cultures were negative. A tuberculin test was negative in the second test strength. Peripheral blood L. E. test at this time was also negative. The following week a few hyaline and granular casts were seen in the urinary sediment, and repeat L. E. tests were done on the blood and marrow. The peripheral blood test showed only a rare L. E. cell, but the bone marrow preparation contained numerous L. E. cells. The patient was started on intravenous ACTH, and in the course of the next month the pericardial and pleural effusions cleared. She gained 25 pounds. Her hemoglobin rose from 8 to 15 gm., and the few abnormal elements in her urine completely disappeared. She has been attending school the past eight months while on a small maintenance dose of cortisone. The patient has had no skin changes or leukopenia at any time during her illness.

Comment: A 16 year old Negro girl initially developed rheumatoid arthritis, cachexia and a normocytic anemia. One year later gastrointestinal symptoms, pleural effusions, bloody pericardial effusion and a slightly abnormal urinary sediment appeared. L. E. cells were finally found, after several negative tests. The response to steroid therapy was dramatic.

Verrucous endocarditis (or Libman-Sacks syndrome) with myocarditis was found in one-third of our 15 autopsied cases. Some hearts may have diffuse myocardial scarring secondary to the arteritis without endocarditis. (Figure 5.) Clinically the heart with either type of lesion acts functionally

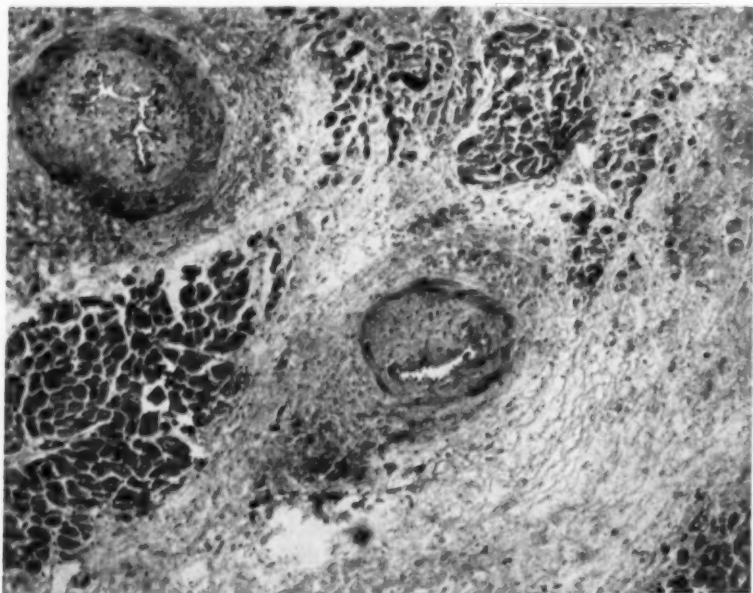


FIG. 5. Arteritis and scarring in the myocardium of a nine year old girl with classic systemic lupus erythematosus. (See also figures 2 and 3.) (85 X.)

like a myocarditis. The earliest change noted is usually a tachycardia well out of proportion to the fever. The heart is diffusely enlarged, often with the point of maximal impulse at the anterior axillary line. A systolic murmur may be heard at the base, soft in quality, and of grade 2 to 3 intensity. Systolic murmurs were present in 26 cases, or 42 per cent. These changes may persist despite the production of a remission and a rise in the hemoglobin to normal as a result of hormonal therapy. No murmurs may be heard even in the presence of endocarditis. A diastolic murmur suggests either secondary bacterial involvement, a marked degree of anemia or a rheumatic

process. A protodiastolic gallop may occur and, in one of our cases, was present almost continually for a year until corrected by special therapy.

If hypertension secondary to lupus nephropathy is present, typical left ventricular failure may ensue; if not, it is common to observe both left and right sided failure, usually of the high output type. Digitalis is of doubtful value. Some adult patients can tolerate 0.3 to 0.4 gm. of digitalis leaf daily for months without toxicity. Mercurials, despite nephropathy, are of the greatest aid. Compound F, which has less mineral corticoid effect than cortisone, may often maintain these cases edema-free.

Pleurisy and pleural effusion were found in 59.5 per cent and 55 per cent, respectively, in this series. Either of these symptoms may be present for years, with recurrences, before any other evidence of the disease appears. They were presenting symptoms in five patients or 8.1 per cent. The following case illustrates this type of pattern.

Case 4. M. Se., a 67 year old white female, was admitted to the hospital in November, 1950, complaining of fever and pleurisy for almost a year. She had apparently been in good health until January, 1950, when pleurisy with fever and effusion appeared. She was hospitalized elsewhere. Two to three thousand cubic centimeters of fluid were aspirated on three different occasions. No diagnosis was made during a three month hospitalization. The patient felt fairly well from April until September, 1950, when there was a recurrence with fever from 99 to 102° F. daily, a tachycardia of 100 to 120, and minimal arthralgia in the hands. An L. E. test was not done at that time. The only abnormal findings on extensive laboratory tests was a white count of 4,800, with normal differential. The patient received several blood transfusions for an increasing anemia. About October 1, 1950, she developed erythematous papules on the dorsum of the hands. A flush on the face and anterior chest appeared several days prior to admission to the Los Angeles County General Hospital on November 20, 1950. Past history revealed that she had been sensitive to sunlight all her life.

The patient was a chronically ill 67 year old woman who had recently lost much weight. There was butterfly and V area facial erythema. The dorsum of the hands showed grouped macular lesions of split-pea size, with scaling and erythema. Skin biopsy of these lesions was interpreted as senile atrophy. Evidence of small left pleural effusion was present. The patient developed a progressive normocytic anemia from 12 to 7.5 gm. in a month. Urinalysis was normal. L. E. cells were present in peripheral blood and bone marrow. After a month's febrile course, convulsions probably due to the lupus appeared. Preterminally she was treated with small doses of ACTH, with effect. Autopsy confirmed the diagnosis of systemic lupus erythematosus.

Comment: This 67 year old woman developed pleurisy with effusion as the first evidence of systemic lupus. She had a spontaneous remission for several months and then relapsed. At this time all the classic changes of lupus were evident. Autopsy confirmed the diagnosis.

Ascites was found in 24.2 per cent, or 15 cases. It does not occur unless there is either congestive failure or nephrotic nephropathy from lupus.

VASCULAR LESIONS

The skin lesions are very pleomorphic and run the entire gamut of the dermatologic field from macules to bullous lesions. Skin lesions may not be present at any time in systemic lupus. This was true in 16 per cent (or 10 cases) of our series. The lesions may be very atypical ones, occurring only in the extremities, as they did in 14.5 per cent (or nine cases). It must be emphasized that the joints are most frequently involved first, and months or years later there may be cutaneous changes, often at a time when there is no joint pain.

The classic erythematous facial blush in the butterfly and V area is well described in all texts. This lesion may never occur during the entire span of the illness. This was true in 20 per cent (or five of the 25 cases that died). In some instances it may be only a transitory erythema of the malar area, which lasts a few days during the course of an illness extending over a period of years. During the acute phase of the butterfly rash, edema of the



FIG. 6. Hyperpigmentation following the facial lesions of lupus erythematosus. Note the increased pigment supraorbitally, in the mustache area, and chin of this 30 year old Mexican woman.

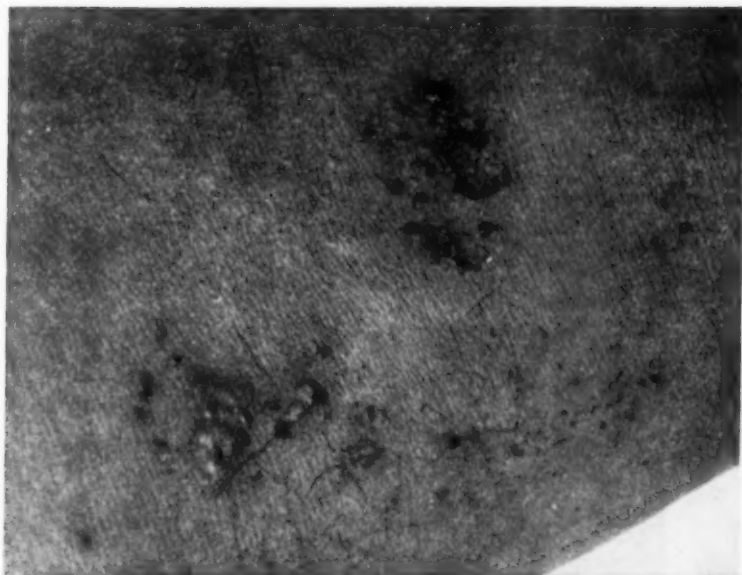


FIG. 7. Atypical vesicular and ulcerative lesions on the foot due to systemic lupus erythematosus.

skin and periorbital tissue is common.¹⁸ This may be confused, by those to whom it is not familiar, with malar and submandibular edema due to the Cushing state induced by therapy. There may or may not be scaling and atrophic scarring of the facial lesions. The acute erythematous blush usually clears without any scarring. Occasionally hyperpigmentation remains. This change due to lupus has not been sufficiently emphasized.² Increased pigmentation may occur diffusely over the body, especially in areas exposed to light, or locally, following lesions. Depigmentation often occurs in healed extremity lesions. Hyperpigmentation was found in 16.1 per cent (or 10 cases). There is usually no change in mucous membrane color, which helps differentiate the cachectic lupus patient from the case of Addison's disease whom she may resemble. (See case 9 below and figure 6.)

Montgomery and McCreight, in a review of 132 cases, stated that one-third of the systemic cases began as discoid forms.¹⁹ In this series, where most of the patients have been drawn from the medical wards, only two cases (or 3.2 per cent) began in this fashion. One was a male who had had discoid lesions for 18 years before they disseminated, with the finding of typical L. E. cells during several months of generalized activity before the systemic disease went into another spontaneous remission.

The peripheral lesions are less well known. These may resemble erythematous papules scattered on the arms and legs which often become depig-

mented when healing. At times, in the acute stages, they may ulcerate and scar (figure 7). Lesions on the hands vary from mottled erythematous macules which blanch on the palms and soles, to papular lesions on the dorsum of the finger which, in advanced cases, may also become necrotic (figure 8). These lesions are most often at the nail-bed, where there is a piling up of many erythematous papules, often purplish in hue. They frequently become secondarily infected.



FIG. 8. Ulcerative hand lesions due to systemic lupus erythematosus.

In the acutely ill, highly febrile patient, miliary vesicles may appear over the trunk and neck. At times these may become bullae.

Ecchymoses and petechial lesions often occur, depending upon the platelet count and other factors involved. (See case 10 below.) The tourniquet test is often positive, due to the active angiitis, even in fairly well controlled cases.¹⁸

Terminally, the facial lesions take on a purplish hue secondary to diffuse hemorrhage into the skin.

Mucous membrane changes were noted in only 11.2 per cent (or seven cases). These usually consist of petechial macules, which become shallow ulcers covered with a dirty grayish base surrounded by an erythematous areola. The lesions are often very painful and the patients cannot swallow. When they are present on the lips they are associated with fissuring, oozing of blood and edema.

Some loss of hair was noted by 70 per cent of the patients specifically asked about it, but it was found in only 24 per cent of the non-interviewed group. It varied from slight thinning to almost complete alopecia. With treatment the hair returns to normal.



FIG. 9. Periphrlebitis in the floor of the third ventricle of the brain of a 13 year old girl with convulsions due to systemic lupus erythematosus. (85 \times .)

Multiple central nervous system manifestations may occur due to the cerebral angiitis.^{21, 22, 23} Figure 1 demonstrates the vascular changes in a spinal cord arteriole. Figure 9 illustrates periphrlebitis in the floor of the third ventricle of a patient with convulsions and mental deterioration due to lupus.

Haserick has described the occurrence of grand mal convulsions for years prior to other changes due to lupus.²² We have found that 35 per cent (or 22 cases) of this series have had seizures, of which 19 (or 30.6 per cent) were due to the disease and three cases (or 4.8 per cent) to the treatment. In only one case was the central nervous system the first system involved.

A description of the means of differential diagnosis has been presented by us previously.¹⁸ Seizures are most common in the terminal phase of the illness. Eleven of 16 patients who died in the hospital had seizures 48 to 72 hours before death. It may be difficult to distinguish between seizures due to the disease and those resulting from hormonal therapy. Fortunately, convulsions caused by ACTH or cortisone do not usually occur during the early treatment phase or before a marked Cushing's state has appeared. If the patient has had a recent exacerbation of the disease, is febrile and normotensive, has a positive tourniquet test and no evidence of a recent weight gain, then the convulsions are most likely due to the disease itself.

Another common terminal event is the occurrence of hemiplegia due to lupus vasculitis, which has been uniformly fatal in our three cases despite vigorous therapy. Severe polyneuritis is uncommon, but myalgia is often present, so that many of these patients are considered to have dermatomyositis. A case of severe polyneuritis due to nutrient artery involvement by lupus has been described.¹⁹ We have seen one such patient.

Signs of meningismus with pleocytosis were found in four cases (or 6.4 per cent). Several of these patients were admitted to the Contagious Disease Division as possible poliomyelitis because of myalgia and meningismus. Lumbar puncture may show several hundred leukocytes, either mostly lymphocytes, or polymorphonuclear leukocytes as well as increased protein.

Case 5. R. D. is an example of this type of change. This 10 year old Mexican identical twin was admitted to this hospital on August 3, 1952, complaining of fever, loss of appetite and joint pain for a month. He had been in fair health until one month prior to admission, when he developed fever as high as 105° F. A few days later a rash appeared on the knees and antecubital fossae, associated with anorexia, weight loss, weakness and malaise. Two weeks prior to admission an x-ray showed pneumonic consolidation, but the patient did not respond to penicillin. He was admitted because of persistent fever and lethargy in addition to the above symptoms.

Past history revealed that he had fractured his skull in 1943, and four years later had developed grand mal epilepsy, which was well controlled on anticonvulsants. His identical twin brother, who has had no head injury, has no seizures. The twin is in good health and has a negative L. E. test. Physical examination of the patient revealed an acutely ill, lethargic 10 year old boy with temperature of 104.6° F., and blood pressure of 110/80 mm. of Hg; respirations, 28 per minute; and pulse, 110. The significant finding was a morbilliform eruption over the entire body which blanched on pressure, with increased erythema over the butterfly area. Several punctate hemorrhages were present on the hard palate. There was mild generalized adenopathy. Small bilateral pleural effusions were present. A soft blowing pulmonic systolic murmur was present in a normal sized heart. The liver was enlarged two fingerbreadths. Neurologic examination was negative, aside from lethargy. Laboratory studies showed a hemoglobin of 9.6 gm.; white cell count, 7,500, with a normal differential; reticulocyte count, 3.6 per cent; icteric index, 14; Wassermann and Kahn, both positive. Urine contained 2 plus albumin, and the sediment showed six to eight hyaline and granular casts per low power field, with occasional red and white cells. Because of his lethargy and a positive serologic test for syphilis, a lumbar puncture was performed, and there were 128 cells per cubic centimeter, all lymphocytes; Pandy, 3 plus; spinal fluid Wassermann, negative. The tap was repeated three days later, with similar findings. Other abnormal laboratory tests were a thymol turbidity of 29 and

cephalin flocculation of 4 plus; albumin, 3.0; globulin, 3.6 gm. per cent. The L. E. test was positive in both peripheral blood and bone marrow. The patient responded dramatically to hormonal therapy. Both Wassermann and Kahn tests reverted after three months' steroid treatment.

Comment: This 10 year old identical twin had a false-positive serologic test for syphilis, somnolence and pleocytosis, in addition to other findings of systemic lupus.

Organic psychoses of all types occurred in 29 per cent (or 15 cases). The majority are due to cerebral vasculitis and clear with hormonal therapy. A few may occur because of the hypopotassemia induced by treatment. In general, the cause of psychoses follows the pattern of convulsive seizures, namely, that if the patient is febrile and the disease active, lupus is the usual cause. In the patient who is being treated with massive doses of ACTH or cortisone, the occurrence of psychoses raises a more difficult problem, and careful studies for hypopotassemia should be made. This condition, if present or even suspected, should be vigorously treated with adequate doses of intravenous or oral solutions of potassium chloride. It may be necessary to give as much as 15 to 25 gm. per 24 hour period if renal function is satisfactory. *In the acutely ill patient, enteric coated tablets are often not absorbed, and this is also true at times in the apparently well controlled case.*

The ocular fundic lesions may be of all types except the deep variety of capillary aneurysm seen in diabetes.²⁰ Lesions were present in one-third of our patients. There is no pathognomonic eyeground picture of this disease. Superficial hemorrhages and exudates appear due to active angiitis. Even hypertensive retinopathy with papilledema may occur due to hypertension from advanced nephropathy or so-called uremic retinopathy in cases with terminal renal failure.

The presence of a renal lesion in this disease is well known. It was found at some stage in a total of 35 cases (56.5 per cent) and in 22 cases (35.5 per cent) at the time of hospital entry. However, it is most important to understand that there is no lesion whose presence is essential to making a diagnosis of lupus. Forty-three and one-half per cent (or 27 cases) never had any urinary abnormalities despite many urinalyses. The author personally has studied fresh sediments from most of these cases initially and during the course of many of them at monthly intervals, and no abnormal elements or proteinuria was ever found.

The nephropathy when present is usually of the nephrotic type. Initially there is the appearance of albuminuria, at times with minimal abnormalities in the sediment. This is followed by a mild increase in blood pressure and the appearance of edema, first of the ankles and then ascites. The latter rarely occurs without either renal or cardiac damage. At this time, the non-protein nitrogen and cholesterol are slightly elevated. As the disease progresses, either massive edema or hypertension may be the outstanding feature.

Systemic lupus may affect the kidney first, as in one case in our series.

Case 6. O. T., a 33 year old white housewife, was admitted to the Los Angeles County General Hospital in July, 1950, complaining of fever and weakness of two months' duration. She had been in good health until eight weeks prior to admission, when she noted easy fatigability, swelling of the ankles, fever, chills and malaise. A physician found albuminuria at this time. Three weeks later she entered another hospital, where an initial diagnosis of nephrosis was made. While she was there a butterfly eruption appeared for the first time and L. E. cells were found. In the few weeks prior to her admissions here, generalized anasarca appeared. Physical examination revealed a pale, chronically ill 33 year old woman with mild anasarca. Temperature was 103° F., pulse, 130; respirations, 20; blood pressure, 120/70 mm. of Hg. The significant physical findings were a maculopapular erythematous eruption, with scattered areas of brownish pigmentation over the butterfly area; 1 to 2 mm. ulcerations throughout the oral cavity, with white, soft membranous surface; soft white exudates in both fundi, and evidence of small bilateral pleural effusions. The liver was enlarged one fingerbreadth. There was 2 plus edema of the extremities. Urinalysis showed a specific gravity of 1.016, with 4 plus albumin and a sediment full of granular and hyaline casts, oval fat bodies and a few red and white cells. Hemoglobin was 13 gm. per cent, which within one week fell to 9.6 gm. The white count was 3,000, with a normal differential. Addis' count revealed 1.1 gm. of protein per 24 hours and 4.1 million granular casts, 1.5 million oval fat bodies, 1.0 million broad casts, and millions of clumped red cells. Nonprotein nitrogen was 40 mg. per cent. The patient released herself from the hospital before therapy was undertaken.

Comment: In the occasional patient, lupus may affect the kidney initially. This may be followed by the other classic changes either immediately or months later.

The following case illustrates how the disease may affect one system, heal, and then affect an entirely different part of the body without a relapse in the first region involved.

Case 7. F. B., a 23 year old white female, was well until June, 1948, when, after sunning herself at the beach, she developed a facial rash with edema of face, hands and feet which lasted a few weeks. The patient had a similar reaction in June, 1949, which she thought was a severe sunburn. About November, 1949, she noted pains in the muscles of the arms, legs and neck, with swelling of the proximal interphalangeal joints. In December, butterfly erythema appeared, with fever up to 102° F. and pleurisy with effusion which lasted about four months, until it was cleared by a three week course of ACTH. Laboratory studies on this admission revealed a hemoglobin of 10 gm. and white count of 2,600. L. E. cells were present. At this time the non-protein nitrogen was 27 mg. per cent, and four urinalyses were normal. No maintenance ACTH or cortisone was given. The patient felt well for 15 months after discharge, until June, 1951, when she began to have aching in the calves and thighs, followed shortly by pain in the proximal interphalangeal joints. These symptoms were mild in degree. In October, 1951, swelling of the ankles appeared and persisted.

Physical examination at this time revealed a well developed and well nourished 23 year old girl who had no evidence of rash or pleural effusion. There was 3 plus soft pitting ankle edema. Blood pressure was 132/85 mm. of Hg. She was afebrile and remained so for the next month that she was followed. Her hemogram was entirely normal. L. E. cells were again present. Urinalysis persistently showed a specific gravity of 1.020 to 1.027, with 3 to 4 plus albumin and an excretion of 6.0 gm. of protein per day. The sediment was filled with red cells and white cells, and numerous red cell casts and coarse granular casts. Nonprotein nitrogen was 51 gm. per cent; cholesterol, 430 mg. per cent; total protein, 5.3 mg. per cent, with albumin of 2.0 mg. per cent.

Comment: This 23 year old woman developed the classic lesions of systemic lupus without renal changes. A remission was induced by a short course of ACTH, and 15 months later nephrotic nephropathy appeared without a relapse in the other systems involved.

Gastrointestinal lesions are very common. These were prominent in 40 per cent of our series (or 25 cases). It was the patient's chief complaint in six cases (or 9.7 per cent) and the first system affected in one case. These symptoms are due to vascular involvement in the bowel wall with infarction or hemorrhage. Often at autopsy the only remnants found are multiple adhesions between loops of bowel. Clinically, in the acute stages it may resemble a surgical abdomen, as in the case below, which was operated upon. Most of the patients have abdominal pain, either cramping or constant, and vomiting, with diffuse direct and rebound tenderness. There is usually no evidence of obstruction, but in one of our cases it was present and cleared with hormonal therapy. Occasionally diarrhea, even of a bloody type, may occur. (See case 9.) In short, the bowel changes, or "gastrointestinal crises" as Osler called them, may mimic any type of abdominal condition. Unless a patient with active systemic lupus has classic signs and symptoms demanding surgery, there is no necessity for operating, since these lesions respond dramatically to ACTH or cortisone.

Arteritis may involve the liver and pancreas (figures 2 and 3). One patient developed severe epigastric pain radiating to the back with vomiting, and a serum amylase of 2,400 units. Autopsy revealed, in addition to the usual changes of lupus, an acute pancreatitis due to the arteritis.

Case 8. G. F. illustrates the clinical and operative picture of these crises and also the insidious development of lupus nephropathy with hypertension. The patient was an 18 year old Mexican girl first admitted to the Los Angeles County General Hospital on January 8, 1951, complaining of exertional dyspnea for two weeks. Studies at that time (reported in detail elsewhere) showed that the patient had acquired hemolytic anemia with a positive L. E. test.²³ There was no evidence of initial involvement of any system other than the hematologic when she was first admitted. The patient responded dramatically to intravenous ACTH therapy. Her hemoglobin rose from 4.0 to 13.1 gm. in nine weeks, and the L. E. test became negative. After several weeks' therapy with ACTH, catheterized urinalysis showed 1 plus albumin, many red cells, numerous granular casts and a few white cells per high power field. These abnormal changes persisted for about a month, until her disease was well controlled by increasing amounts of the hormone. Then the urine became normal again. She was discharged from the hospital on cortisone, 25 mg. every eight hours. The patient was in a good remission until July, 1951, when, after an exposure to the sun, she developed a mild butterfly erythema with some erythematous splotches on the legs, both of which cleared in about a week. Her blood pressure was 120/85 mm. of Hg. Urinalysis at this time showed 5 per cent albumin (wet). The sediment contained many red cells and few white cells. There were no casts. Cholesterol was 198 mg. per cent; albumin, 4.3 gm. per cent; globulin, 2.1 gm. per cent; nonprotein nitrogen, 33 mg. per cent; hemoglobin, 14.5 gm. The patient refused hospitalization at this time and did not even return to clinic. She was admitted two months later, in December, 1951, complaining of abdominal pain, nausea and vomiting of one day's duration. Two weeks prior to this admission the patient had noted increasing ankle edema and had stopped her maintenance dose of cortisone. During this period her ankle edema de-

creased. The day prior to admission she suddenly developed severe colicky epigastric pain which at times was generalized, with watery diarrhea. She became nauseated and vomited numerous times. There was no blood in stool or vomitus. The pain in the course of the next few hours localized in the right lower quadrant.

Physical examination revealed an acutely ill 18 year old Mexican girl who was well developed and well nourished. The significant findings were limited to the abdomen, where there was no distention. The bowel sounds were hypoactive and there was tenderness throughout the right side, especially in the right lower quadrant, where increased rigidity was present. Rebound tenderness was felt throughout, with radiation to the right lower quadrant. Pelvic examination showed increased tenderness in the right adnexa. Laboratory tests revealed white blood cells of 10,500, with 88 per cent polymorphonuclear leukocytes; reticulocytes, 1.8 per cent; platelets, normal on smear; hemoglobin, 8.5 gm. Catheterized urine was brownish in color, with a specific gravity of 1.023; albumin, 3 plus. There were 5 to 10 casts per low power field of the fine and coarse granular types. Five to 10 white cells and 40 red cells were found per high power field. Nonprotein nitrogen was 51 mg. per cent; albumin, 3.9; globulin, 2.2. Laparotomy was performed. The appendix was grossly and microscopically normal. Two thousand cubic centimeters of clear colorless fluid were aspirated from the peritoneal cavity. The entire ileum, except for the distal 8 cm. and the distal one-half of the jejunum, was diffusely hemorrhagic, more marked on the antimesenteric border. The hemorrhagic area was made up of many petechiae, and blood was wiped from the serosal surface of the bowel. There was also moderate edema of the small bowel mesentery. No lymph nodes were enlarged. Liver, gallbladder and pelvis were normal. The patient was placed on 40 units of intravenous ACTH per day and in a few days the abdominal symptoms disappeared. The patient released herself from the hospital and was not seen for another six weeks, when she returned to clinic with a history of having taken 100 to 150 mg. of cortisone and of not adhering to a low sodium diet. Her blood pressure was 180/120 mm. of Hg and she had 4 plus ankle edema. Immediate admission was advised but she refused, only to be brought in the following day in a postconvulsive stupor after a series of grand mal seizures. At this time her nonprotein nitrogen had risen to 63, cholesterol to 317, and albuminuria to 4.2 gm. per day. The hypertension gradually increased to 220/140 mm. of Hg, despite 30 mg. of intravenous nitrogen mustard, and the renal damage progressed. The patient died in April, 1952, of hypertensive encephalopathy secondary to the nephropathy of her systemic lupus erythematosus. There was little change in her blood chemistry from that previously recorded. Permission for autopsy was denied.

Comment: This 18 year old girl developed acquired hemolytic anemia as the first symptom of systemic lupus. This was well controlled when the patient took her medication. During the course of the next year she developed skin lesions in one relapse and an acute abdomen in another relapse. Laparotomy revealed a diffusely hemorrhagic small bowel, and her symptoms responded to the reinstitution of hormonal therapy. Perhaps because of her erratic control, lupus nephropathy developed and progressed to a fatal termination in hypertensive encephalopathy.

Adenopathy occurs more frequently in children than in adults, where it is minimal to absent. It was present in 42 per cent (or 26 cases).

The frequency of splenomegaly has been overrated. We found it in 8.1 per cent (or five cases) at some time during the illness. It is usually present with hepatomegaly when there is a severe hemolytic anemia due to lupus.

Hepatomegaly occurred in 34 per cent of the entire series. It may be present without congestive failure or anemia.

Raynaud's phenomenon is a very frequent abnormality which has been little emphasized in this disease. It was present at some time in 25.8 per cent of all the cases, and in 35 per cent of 37 patients specifically questioned about it. In our experience, once present, it usually persists despite therapy, although Soffer does not agree.²⁴ This phenomenon is a nonspecific one and may occur for years prior to the development of other changes due to lupus, scleroderma or dermatomyositis. Often it is the symptom of a collagen disease and not an entity. In five cases (or 8.1 per cent) it was the first manifestation of systemic lupus. The following case illustrates the initial appearance of Raynaud's phenomenon prior to the appearance of other changes.

Case 9. F. K., a 30 year old white female, was first admitted to the Los Angeles County General Hospital in September, 1952, complaining of tarry stools for five days. The patient had been in good health until three years prior to admission, when she had noted the appearance of sensitivity of her hands to cold. Initially they would turn white and then blue. Associated with this was a tingling sensation. Seventeen months prior to admission, when six months pregnant, she had developed arthralgia in the knees. This persisted until delivery and did not recur. There was profuse bleeding for seven days postpartum, and a curettage had to be performed to stop it. She did not menstruate after that procedure. Four weeks after parturition, daily spiking temperatures and generalized weakness appeared. At about this time she noted that the skin over her entire body was turning a muddy color. Ten months prior to admission she had an episode of nausea, vomiting and diarrhea for three weeks, without much abdominal pain. The patient was hospitalized at that time, but no specific diagnosis was made. Since then, there have been persistent anorexia, a steady weight loss of 20 pounds, alopecia and increasing weakness. Three months before admission she received eight blood transfusions for a refractory anemia. At erratic intervals her temperature often spiked. For three months prior to admission she also had arthralgia in the proximal interphalangeal joints, with inability to close her fist. Because of the diffuse pigmentation and cachexia she was treated on the outside for Addison's disease. Five days prior to admission the patient began to pass tarry stools, and the following day bleeding appeared from the gums. Both of these symptoms persisted until admission.

Temperature was 100° F.; pulse, 120; respirations, 22; blood pressure, 120/76 mm. of Hg. The patient was a chronically ill, emaciated 30 year old woman who had a diffuse hyperpigmented muddy gray color throughout her body, most marked on the dorsal surfaces of the extremities and absent on the mucous membranes. A grade 3 systolic murmur was present in the pulmonic area. The fingers could not be closed fully. There was induration of the skin of the dorsum of the fingers of both hands below the normally appearing proximal interphalangeal joints. The skin had a sclerodermatous feel, but this gradually improved during the next few weeks in the hospital. Laboratory studies showed a hemoglobin of 3.8 gm.; with a white count of 10,200 and a normal differential. Urinalysis was normal. Bleeding time was 3.5 min.; clotting time (Lee White), 6.5 min., with good clot retraction; platelet count, 298,000; reticulocyte count, 9.3 per cent. A few days after admission her stools became guaiac-negative. X-rays of the gastrointestinal tract were normal. Two peripheral blood L. E. preparations were negative during the first weeks in the hospital. At about this time the patient became febrile, with temperatures up to 104° F.

daily. Marked myalgia appeared in the legs, with hyperesthesia to pain. (See muscle biopsy, figure 4.) The sclerodactyly of the fingers improved. Another L. E. preparation on peripheral blood was done, and this showed a few typical cells. The bone marrow L. E. test contained many L. E. cells, which confirmed the diagnosis. Unfortunately, at this time the patient weighed 66 pounds and was moribund. Hormonal treatment was of no value. A repeat peripheral blood L. E. preparation several days prior to death was negative. Autopsy confirmed the diagnosis of systemic lupus. The gastrointestinal tract appeared normal at postmortem examination.

Comment: This 30 year old woman developed Raynaud's phenomenon two years prior to the appearance of hyperpigmentation and other changes due to systemic lupus.

HEMATOLOGIC CHANGES

Hematologic changes in systemic lupus are well known.²⁵ Leukopenia was noted at some time in 68 per cent (or 42 cases). We have considered this to be present if only one count on the record was below 4,500. At times there may be only one leukopenic level in dozens of tests. A white count below 2,000 with few granulocytes is distinctly unusual in systemic lupus, and other diagnoses must be considered.

Anemia (hemoglobin below 11 gm.) was present in 77.5 per cent (or 48 cases). It is usually normocytic in type, and most cases are hemolytic in nature when the anemia is marked, unless uremia is present.²³ Four patients (or 6.4 per cent) had classic acquired hemolytic anemia as their presenting symptom. The author has been told of several other cases since this report appeared.

Thrombocytopenia is often present and may lead to hemorrhagic phenomena in association with the active angiitis usually present. Cases have been described of classic idiopathic thrombocytopenic purpura with a good response to splenectomy who, years later, develop systemic lupus, and restudy of their spleens shows the classic onion-skin change of lupus.²³

The bone marrow is usually active to hyperactive, depending on whether hemolysis is present.^{23, 26} In our experience it is never hypocellular. The syndrome of "hypersplenism" well described the mechanism of the blood changes in many patients with this disease.²³

Haserick has recently emphasized the initial occurrence of a false-positive serologic test for syphilis prior to the development of other evidences of systemic lupus erythematosus.²⁶ Moore pointed out that a biologic false-positive test for syphilis is a serious thing, which should be followed up until its cause is determined.²⁷ Nineteen patients in our series (or 32.6 per cent) had a positive serologic test for syphilis at some time during their illness. Of these, two apparently were true positives. An interesting aspect of this reaction is that, of 17 patients with probable false-positive serologic tests for syphilis, 14 had positive L. E. tests. In one of the remaining patients the test was not done. Twenty-seven cases had positive L. E. tests with negative serologic tests for syphilis. In 15 additional cases both tests were

negative. There was no correlation between hyperglobulinemia and a positive Wassermann reaction. L. E. cells were demonstrated in 13 out of 15 patients with hyperglobulinemia or 86.5 per cent.

Conley recently described two cases of a hemorrhagic disorder caused by a circulating anticoagulant in lupus.²⁸ The case which follows demonstrates a similar disturbance in clotting as well as the presence of abnormal serologic tests. It is the only hemorrhagic syndrome of this type we have seen.

Case 10. E. Z., a 46 year old Mexican woman, was admitted to the Los Angeles County General Hospital on February 3, 1952, complaining of vomiting of 10 days' duration. She had been in good health until her admission to hospital in 1943. The patient had had five previous admissions to the obstetrical service of this hospital, at two year intervals, with normal deliveries and negative serologic tests for syphilis. In 1943 she was re-admitted because of a thrombophlebitis of the leg. A positive Kahn and negative Wassermann were noted, without any history of exposure. The patient was referred to the Venereal Disease Clinic where, during a two year course of heavy metal therapy, there were numerous references on the records to arthralgia. Lumbar puncture at the end of treatment was normal. In 1946, the Mazzini test was negative. In 1950, both Kolmer and Kahn were negative. During her final admission the Kolmer again became positive and the Kahn remained negative.

For one year prior to her last admission the patient complained of a recurrence of arthralgia in the hands, elbows and shoulders. Her hemogram was normal at this time. There was no evidence of rheumatoid deformity on physical examination or x-ray. The hands were diffusely swollen, without evidence of erythema. During the past few months she had had frequent night sweats and a 15 pound weight loss. Ten days prior to admission she developed cramping epigastric pain and vomited all ingested food. After the first day her vomitus became blood-tinged. Recurrent nose bleeds appeared at this time.

Physical examination revealed an acutely ill, 46 year old Mexican woman with temperature of 101° F., pulse, 120, respirations of 24 and blood pressure of 125/60 mm. of Hg. There was bleeding from the nares, and the septal mucosa was atrophic with pinpoint bleeding areas. The lips were fissured and there was bleeding from the corners of the mouth. There was a grade 2 blowing systolic murmur at the left sternal border which was transmitted throughout the precordium. The heart was normal in size. The liver was percussed down three fingerbreadths below the costal margin. There was moderate tenderness in the right flank and upper quadrant. Laboratory studies revealed a hemoglobin of 4.1 gm. and red cell count of 1.3 million; hematocrit, 20; white count, 7,800 per cubic millimeter, with a normal differential. The red cells were slightly macrocytic, with moderate anisocytosis. Agglutination of red cells was seen on smear. The platelets were reduced; reticulocytes, 19.4 per cent; bleeding time (Duke), 7½ min.; clotting time (Lee-White), over 24 hours; prothrombin content, 110 per cent; fibrinogen content, normal. Unfortunately, no specific studies for increased circulating anticoagulant were done. Cold agglutination was positive in 1-40 dilution; Coombs test, negative direct and indirect; urine urobilinogen, positive in a 1-10 dilution. The L. E. preparation showed marked erythrophagocytosis in addition to many typical L. E. cells. Bone marrow smear was compatible with a hemolytic anemia. Icteric index was 16; nonprotein nitrogen, 48; total protein, 8.0 gm., with an albumin of 4.2. Catheterized urine showed a specific gravity of 1.013, 1 plus albumin, 1 to 2 granular casts per high power field, occasional hyaline casts, 10 to 12 white cells per high power field, and occasional red cells. Kolmer was positive, Kahn negative.

The patient ran a downward course despite transfusions and increasing amounts of intravenous ACTH which, on the last few days, was 200 units per 24 hours. She continued to ooze blood, and died three weeks after admission. Preterminally, the patient's face developed the diffuse brownish purple hue often seen in terminal lupus.

At autopsy, numerous petechial hemorrhages were scattered over the entire body, especially on the upper extremities and trunk. Large ecchymoses, measuring up to 20 cm. in diameter, were present over both arms and legs. Verrucous endocarditis was present on the aortic valves. The spleen was enlarged and weighed 430 gm. Microscopic study of kidney, heart and spleen showed the classic lupus changes.

Comment: This 46 year old woman developed a positive serologic test for syphilis as the first evidence of her systemic lupus. It was followed during the next nine years by other changes due to the underlying disease, which had remissions and exacerbations. Terminally she developed a hemorrhagic phenomenon, perhaps due to an increased amount of circulating anticoagulant.

L. E. CELLS

Since Hargraves described the L. E. test it is possible to group a large number of vague, previously undiagnosed syndromes into one disease pattern, into which they fit very well. Some workers question the pathognomonic character of the L. E. test.²⁹ In our experience of several thousand tests on all diseases at this general hospital, we have never found a false-positive. There are scattered reports of one case of various ailments in which a positive test was found, but the author feels that if typical L. E. cells are present at some time in the patient's illness he will, if he lives long enough, develop the pattern of the disease which we have attempted to describe. Most of the reports of false-positive tests have been only acute studies, without prolonged patient follow-up or thorough study to rule out variants of lupus. Autopsy may not be of help, since the postmortem changes in many cases of typical clinical lupus may be minimal or absent, especially in the more acute ones.

In 19 cases (or 32.6 per cent of our series), L. E. tests to date have been negative and in two patients they were not done. The diagnosis was proved in the 21 patients as follows: autopsy in six patients, classic skin and systemic changes in six, positive skin biopsy in four and typical clinical picture in five.

Eight patients (or 12.9 per cent) had no L. E. cells found on admission or on previous outside studies. By doing repeated tests over the next few weeks to a year or more that these patients were followed, L. E. cells were finally demonstrated in each case.

If the peripheral blood L. E. test is negative in a patient in whom systemic lupus is strongly suspected, then a bone marrow smear and L. E. test must be performed, because in about 5 per cent of patients this test may be positive while the peripheral blood examination is negative.³⁰

The response to therapy in this group of cases, which might be termed variants of lupus, is striking. Other collagen diseases which may resemble lupus, such as scleroderma, dermatomyositis and thrombotic thrombocyto-

penia, are not significantly helped by the newer hormones. Hence it is important to make a specific diagnosis, and never to use the term "collagen" disease as a diagnostic label.

It should again be emphasized that systemic lupus may affect any system initially, heal, or progress, and then immediately or years later affect another area. There is no system that must be involved for a diagnosis to be made, as we have tried to point out. In individual cases during the course of years, no urinary abnormalities may be found despite careful study, and also no leukopenia, anemia or L. E. cells. In apparently typical cases, with classic skin lesions and multiple system involvement, L. E. cells may not be found, or may be noted only after dozens of tests and several years of follow-up study.

The only way in which the question of the false-positive L. E. test can be solved as well as the study of the breadth of systemic lupus is by the routine performance of these tests on all cases which show the types of involvement we have described. If the test is positive, or if the patient fits into the clinical group of lupus, then she must be followed with repeated studies over the years.

In all patients in whom any one of the collagen diseases is suspected L. E. cell studies of both peripheral blood and marrow should be made. In our experience, the heparinized peripheral blood technic which we use (and will describe in a later paper) is as good as the more complicated bone marrow test, except in occasional cases, as we have indicated above.

DISCUSSION

An attempt has been made to present the various modes in which systemic lupus may begin, and to emphasize the fact that any system may be initially involved, and may heal or progress, and years later involvement may occur in that same system or in an entirely different one, without relapse in the region initially involved. It is most important to understand the vagaries of this illness, which does not tend to progress uniformly in all organs simultaneously, and which is subject to remissions and exacerbations in 39.7 per cent of cases.

In evaluating a patient, the history of pleurisy and effusion years ago, thrombocytopenic purpura, pericarditis, epilepsy, rheumatoid arthritis, a positive serologic test for syphilis, etc., may merely be part of the pattern of systemic lupus affecting another organ. When these are thought of in the light of his current illness, it may become apparent that they fit into the pattern of systemic lupus. Multiple blood and bone marrow L. E. tests must be performed on such a case to confirm the diagnosis.

It is only when the medical profession will forget the textbook picture of this disease, and realize that it is half as common as acute rheumatic fever and more common than pernicious anemia, that it will be correctly diagnosed. In our opinion the prognosis is good, especially with early diagnosis and

therapy prior to involvement of the central nervous system and advanced renal damage. The high percentage of deaths in this series is felt to be due to the small doses of hormones utilized in the treatment of the first 20 cases, and to the fact that county hospital cases are far advanced at the time of admission.

SUMMARY

Systemic lupus erythematosus is a common disease which is one-half as frequent as acute rheumatic fever at this hospital. An analysis of the clinical picture of 62 cases seen by the author during the past two and one-half years has been presented.

Since Hargraves described the L. E. test five years ago there has been a profound change in the breadth of the concept of this disease, which is subject to remissions and exacerbations in 39.7 per cent of the patients. Any system may be initially involved, and heal, and months to years later another region may be affected without a relapse in the first part affected. This concept is fundamental to an understanding of the disease process.

A series of patients has been described showing the initial involvement of different organs in each case, with emphasis on beginning lesions in the gastrointestinal tract, pericardium, kidney, peripheral blood vessels, pleura, central nervous system and hematologic systems.

Hormonal therapy has been the greatest advance in treatment of these cases to date. We have shown that, with adequate early therapy, the abnormalities can be reversed. It is essential, therefore, that these cases be recognized early, prior to irreversible damage. It is to that end that this paper has been written.

ACKNOWLEDGMENT

The author wishes to thank Dr. Paul Starr, Professor of Medicine, University of Southern California Medical School, for his helpful advice, coöperation and criticism of this work and Mr. Lloyd Matlovsky, Chief of the Photographic Department of the Los Angeles County General Hospital, for his assistance.

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CASE REPORTS

INSULIN-RESISTANT DIABETES MELLITUS ASSOCIATED WITH HEMOCHROMATOSIS *

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THE amount of insulin required for the control of diabetes varies markedly. The insulin requirement is usually increased in the presence of infection, acidosis and coma, and often in association with endocrinopathies, liver disease, hemochromatosis and neoplasm. Furthermore, the insulin requirement of adolescent diabetics may be high and variable. Patients requiring over 200 units of insulin per day are generally considered as "insulin-resistant."¹

Some cases of insulin resistance have no associated condition to which the resistance can be attributed. The serum of such cases of "idiopathic" insulin resistance may neutralize insulin in a manner consistent with the presence of an antibody for insulin. Some cases of resistance also manifest allergic reactions, but these two conditions—resistance and allergy to insulin—may occur independently.

The case to be presented had a high degree of resistance to commercial insulin and a less marked resistance to human insulin. There were no allergic reactions to therapeutic injections of insulin, but endermally injected insulin, whether commercial or human, produced a wheal and erythema, and skin-sensitizing antibody was demonstrated in low titer for both insulins. The patient's serum protected mice against the hypoglycemic action of insulin. Hemochromatosis was not recognized during life but was found at autopsy.

CASE REPORT

A 68 year old retired white male entered Boston City Hospital on May 25, 1950, with the complaint of bilateral leg weakness of two weeks' duration. Three years earlier bilateral cataracts, glycosuria and fasting hyperglycemia were found at another hospital. The patient was given a low carbohydrate diet and 20 units of protamine zinc insulin daily, with control of the diabetes; and an iridectomy was performed.

Two years before admission he had been hospitalized for a second iridectomy and again was adequately controlled with 20 units of protamine zinc insulin daily. The hospital stay and postoperative course were without complication. After discharge he showed mild to moderate fasting glycosuria. During the year prior to admission to this hospital, the patient ceased taking insulin regularly. In the six months before entry there was a loss of 40 to 50 pounds in weight, generalized weakness and

* Received for publication November 1, 1952.

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Since Dr. Eskind is at present in the service, requests for reprints should be addressed to one of the other authors at the Evans Memorial, 65 East Newton St., Boston 18, Mass.

fatigability. For two weeks just prior to entry there was a marked increase in weakness of the legs, unaccompanied by numbness or tingling, but so severe that he was no longer able to move about his home.

Since the institution of insulin therapy there had been no episodes characteristic of spontaneous or induced hypoglycemia, nor episodes of acidosis. There was no history suggestive of infection, jaundice, abnormal skin pigmentation, allergic disease or blood transfusions. The patient had used alcoholic beverages in moderation.

The family history was noncontributory. The patient lived alone and prepared his own meals.

Physical examination on admission revealed a thin white male who showed marked evidence of weight loss and who appeared chronically ill. The temperature was 99.8° F. (rectally); the pulse, 100; the respirations, 20. The blood pressure was 160/90 mm. of Hg. The skin was dry and loose with loss of subcutaneous fat. There was no pigmentation of the skin, mucous membranes or sclerae, and the ears, nose and throat were not remarkable. The eyes showed bilateral iridectomy scars, with the irregular pupils reacting well to light and with accommodation. Fundusoscopic examination showed grade I retinal changes. The neck was supple, and there was no lymphadenopathy or evidence of venous congestion. The shape of the chest suggested emphysema. The lung fields were clear to percussion and auscultation. The heart was not enlarged and no murmurs were heard. A soft liver edge was felt 1 cm. below the right costal margin. Spleen and kidneys were not palpable. The rectum and genitalia were normal. The patient demonstrated some unsteadiness of gait, but there was no muscular weakness or tenderness of the extremities. Slight memory defect for recent events was demonstrated. Sensory perception was intact. Right facial weakness was present, but there was no evidence of other cranial nerve abnormality. The deep tendon reflexes were hypoactive and the ankle jerks were absent. An extensor plantar response was present on the right. The Romberg test was negative.

With the exception of marked glycosuria, the urine was normal. Urine culture showed no growth. The excretion of phenolsulfonphthalein was 50 per cent in two hours. The hemoglobin was 14.5 gm./100 c.c. and the hematocrit was 44 per cent. The sedimentation rate was 20 mm./hour. The white count was 9,000, with 78 per cent polymorphonuclear cells and 22 per cent lymphocytes. The Hinton test was negative. The blood urea nitrogen was 20 mg./100 c.c. The blood sugar was 560 mg./100 c.c. The carbon dioxide combining power was 46 vol. per cent. The serum cholesterol was 272 mg./100 c.c. In three tests the bromsulfalein remaining in the serum was 4 per cent, 4 per cent and 6 per cent after 45 minutes. The formol gel and the cephalin flocculation tests were negative. The prothrombin time was 100 per cent. The 24 hour 17-ketosteroid excretion was normal. An eosinopenic response² followed the injection of epinephrine. The basal metabolic rate was minus 19. X-ray of the chest showed evidence of bilateral apical fibrosis and calcification consistent with old inactive pulmonary tuberculosis. The spinal fluid contained 59 mg./100 c.c. of protein but was otherwise normal.

Course: Because of evidence of marked weight loss and undernutrition, the patient was placed on a diet containing 2,600 calories, given in four feedings.

Twenty-five units of regular insulin given subcutaneously on the first day produced no change in the blood sugar level or the glycosuria. Thereafter, the daily dose of insulin was gradually increased, as shown in figure 1.

By the end of one month the daily dose of insulin had been increased to 170 units of protamine zinc insulin before breakfast, and 150 units of regular insulin given as pre-meal supplements. However, the patient continued to show 4 plus glycosuria, without acetonuria, and the fasting blood sugar ranged from 250 to 350 mg. per cent.

After two months in the hospital the patient's total daily dose was 470 units per

day; glycosuria persisted and the fasting blood sugars were 300 to 400 mg. per cent. By the seventy-eighth hospital day the daily dose of insulin had reached 720 units, and there was still no change in the glycosuria or blood sugar.

At this time, treatment with protamine zinc and regular insulin was discontinued and a special concentrated regular insulin containing 500 units per cubic centimeter (U. 500) was substituted.*

The patient was given an initial subcutaneous dose of 600 units of U. 500 insulin, supplemented by 100 units of regular (U. 40) insulin during the day because of persistence of marked glycosuria. Within two days the total daily insulin dosage was increased to 1,050 units. On the following day, and for the first time, the patient

COURSE UNDER TREATMENT WITH INSULIN

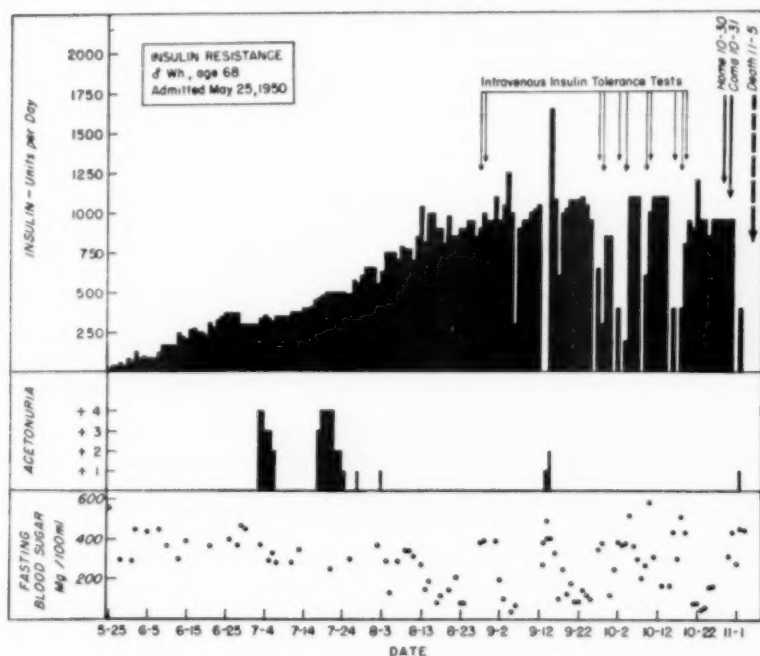


FIG. 1.

had a fasting blood sugar below 200 mg. per cent and the morning urine specimen gave a green reaction for sugar. In the following 18 days the insulin dosage ranged between 750 and 1,000 units, averaging 900 units, and repeated fasting blood sugars contained less than 200 mg./100 c.c., and the pre-breakfast urine test for sugar gave a blue or green reduction.

During the remaining 60 days of the patient's hospital stay control of the diabetes was difficult because, in the performance of the intravenous insulin tolerance tests to be described below, insulin was withheld for 24 hours immediately preceding each

* Kindly supplied by Dr. W. R. Kirtley, of Eli Lilly Co., Indianapolis, Indiana.

test. This was done to avoid hypoglycemic reactions from the large doses of insulin given on these occasions. This deliberate omission of insulin explains the great fluctuations in the fasting blood sugars (figure 1).

On one occasion, in order to see to what level the blood sugar would rise, insulin was withheld for two days (September 14 and 15). After 56 hours the blood sugar was 413 mg. per cent and the blood carbon dioxide was 52 vol. per cent, and there was a trace of acetone in the urine. In the subsequent 48 hours the patient received 2,730 units of insulin, and the blood sugar fell to between 100 and 150 mg./100 c.c., and the urine gave a green test for sugar.

During the uninterrupted administration of insulin in the nine days before discharge, mild hypoglycemic reactions were noted for the first time. These followed the subcutaneous administration of 1,100 and 1,150 units on two consecutive days. When the supplementary afternoon insulin was omitted and the patient was given 950 units in a single dose every morning, the fasting blood sugar was between 150 and 200 mg. per cent and he had no further hypoglycemic reactions.

As the patient was very eager to go home, he was discharged on the one hundred ninetyeth hospital day with instructions to take 950 units of U. 500 insulin every morning and to make no change in his diet. As the patient had had several hypoglycemic reactions during hospitalization, he was familiar with this complication. He was further instructed to keep sugar on hand at all times.

When the patient was seen in the afternoon three days after discharge he stated that all tests for sugar in the urine had given a green reaction. He was told to reduce the dosage of insulin on the next morning and he returned to his home, where he was seen by his daughter at 5 p.m. He was found eight hours later lying on the floor of his apartment, cold, sweaty and completely unresponsive. His evening meal was still cooking on the stove, and a half-eaten candy bar was on a table near him.

Upon arrival at the hospital emergency ward he received an intravenous injection of 50 c.c. of 50 per cent glucose. A blood sugar drawn 15 minutes later was 50 mg./100 c.c. The patient was semicomatose and could be aroused only by painful stimuli. The skin was cold and clammy and the pulse thready, with a rate of 120. The blood pressure was 130/86 mm. of Hg. A slight bruise was present over the right frontoparietal scalp. There was no blood in the nose and no discoloration of the drums. The pupils were reactive to light and of equal size. There was no neck stiffness, and the only localizing neurologic signs present were facial weakness and an extensor plantar response, both on the right and both having been present at the time of the patient's first admission.

He received multiple intravenous infusions of 20 per cent glucose, and the blood sugar two hours later was 350 mg./100 c.c. In spite of this he remained semicomatose. Stereoscopic films of his skull were taken and no fractures noted. Lumbar puncture shortly after admission yielded bloody fluid, presumably due to technical difficulties in placing the needle. The blood urea nitrogen was 20 mg./100 c.c., the urinary output was adequate, and the urine was free of acetone. No insulin was given until the second day when, because of mild acetonuria, he received 400 units of regular insulin intravenously. Within one hour the acetonuria disappeared, though unassociated with a significant change in the blood sugar level, which had ranged between 300 and 400 mg./100 c.c.

On the fourth day the patient developed marked nuchal rigidity and rapid, deep respirations. The blood urea nitrogen was 51 mg./100 c.c., the carbon dioxide combining power was 40 vol. per cent, the chloride was 100 mEq./L., and the blood sugar was 445 mg./100 c.c. The patient's temperature gradually rose to 105° F. (rectally), and râles appeared in the right lower posterior chest. Penicillin was given but the respirations became more labored and he died on the sixth day.

Postmortem Findings *: External examination revealed the skin to be clear of abnormal pigmentation, as was the buccal mucosa.

There were bilateral posterior adhesions at the lung apices, and beneath this area was seen mottling of the lung parenchyma. No cavitation or caseation was present, and there were no areas of consolidation. The heart was not remarkable save for slight thickening of the aortic valve cusps.

The peritoneum was smooth and glistening throughout, and there was no free fluid. The liver weighed 1930 gm., and its edge extended 4 cm. below the xiphoid in the midline and was at the level of the costal margin in the right midclavicular line. The capsule was smooth and opaque, and in some areas there was a fine nodularity to the surface of the liver.

On cut section, the liver parenchyma was homogeneous and brown, and of markedly firm consistency. The gall-bladder, bile ducts, spleen and gastrointestinal tract were normal. The pancreas was of normal shape, though somewhat small, weighing 37 gm. On cut section the parenchyma was buff-colored and of normal consistency, and showed the usual lobular architecture. There was no evidence of inflammation or fat necrosis. Grossly and on cut section the kidneys were normal. The adrenals were of approximately normal size, with a combined weight of 14.5 gm. On cut section the cortex and medulla appeared normal. The genital organs were not remarkable.

The skull and leptomeninges were not remarkable.

The brain weighed 1,210 gm. and was symmetrical and firm, without external discoloration or softening. The cerebral vessels showed only moderate arteriosclerosis.

Microscopic Examination: The lungs showed evidence of old fibrous and calcified tuberculosis in both apices. There was also bilateral basilar pneumonia. Ziehl-Neelsen stain of the apical tissues showed no acid-fast organisms. Cultures of the basilar areas grew out hemolytic *Staphylococcus aureus* and *Hemophilus influenzae*.

There was a moderate increase of the fibrous tissue of the portal veins. Many of the hepatic cells, particularly in the vicinity of the central veins, contained one or more clear vacuoles, as well as large amounts of brown, granular pigment. This same pigment was to be seen in the epithelial cells of some of the bile ducts. On iron stain these pigment granules appeared blue-black.

Some of the parenchymal cells of the pancreas contained dark pigment granules, and on iron stain these were blue-black. The islet tissue was not diminished in quantity and was not abnormal in appearance.

Regular hematoxylin and eosin stain of the adrenals revealed no abnormality, but iron stain showed the presence of blue-black granules in a few cells of the glomerulosa.

Routine and special iron stains of the skin, kidneys, testes, pituitary and spleen were not remarkable, and showed none of the characteristic granular pigmentation.

Final anatomic diagnoses were: (1) Hemochromatosis involving liver, pancreas, and adrenals. (2) Arteriosclerotic heart disease. (3) Healed apical tuberculosis, bilateral. (4) Bilateral basilar bronchopneumonia.

SPECIAL STUDIES

Materials and Methods: All dilutions of insulin and serum for skin testing were made with 0.85 per cent salt solution. Skin tests were done on the arm or the back with a volume of approximately 0.02 c.c. injected endermally. For

* Autopsy performed by Dr. Roger Gilchrist, of the Mallory Institute of Pathology, Boston City Hospital.

the detection of skin sensitizing antibody, skin sites were prepared 24 hours before testing with 0.1 c.c. of diluted or undiluted serum injected endermally.

The human insulin used in these studies has been described in an earlier publication.³ When assayed in mice and rabbits at the time of preparation it contained 24 units/ml. In the course of studying the patient reported here, it became clear to us that the preparation had lost one-half or two-thirds of its original activity during storage for two and one-half years in the icebox.

The tests for insulin-neutralizing activity were done in mice (which had been starved for 18 hours) by injecting intraabdominally 0.5 c.c. of a mixture containing equal parts of serum appropriately diluted and a solution of insulin. A normal serum to which glucose was added to equal that in the patient's serum served as a control. The mice were put in a step-in incubator at 37° C. and observed for two hours for the appearance of signs of hypoglycemia. These included marked unsteadiness of gait, marked weakness or paralysis of hind limbs, convulsions or death.

Skin Tests: An endermal test with a solution containing 4 units/ml. of regular insulin (Iletin, Lilly) gave a strongly positive reaction (wheal measuring 0.75 cm. and erythema measuring 3 cm.) within 15 minutes. Serial dilutions of regular

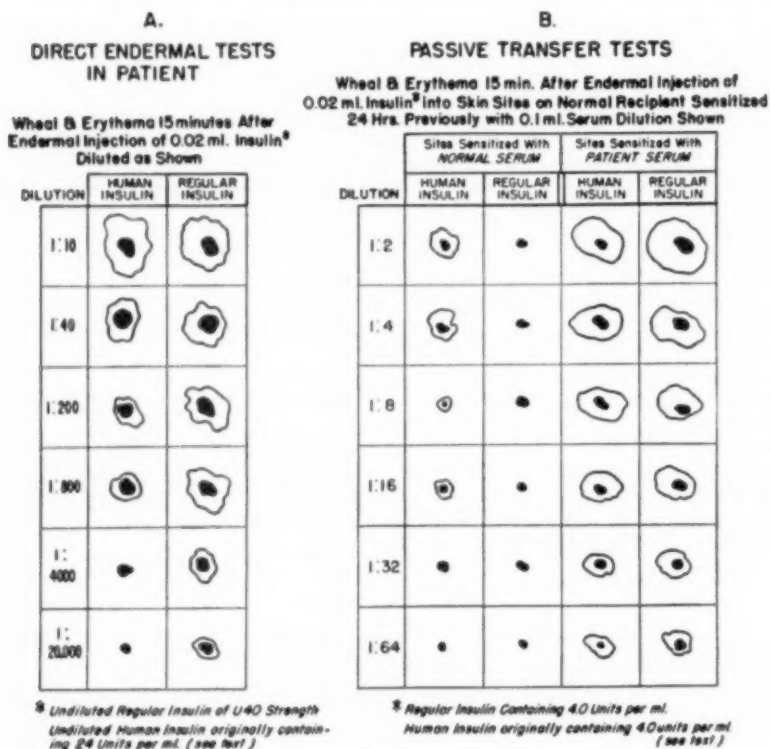


FIG. 2.

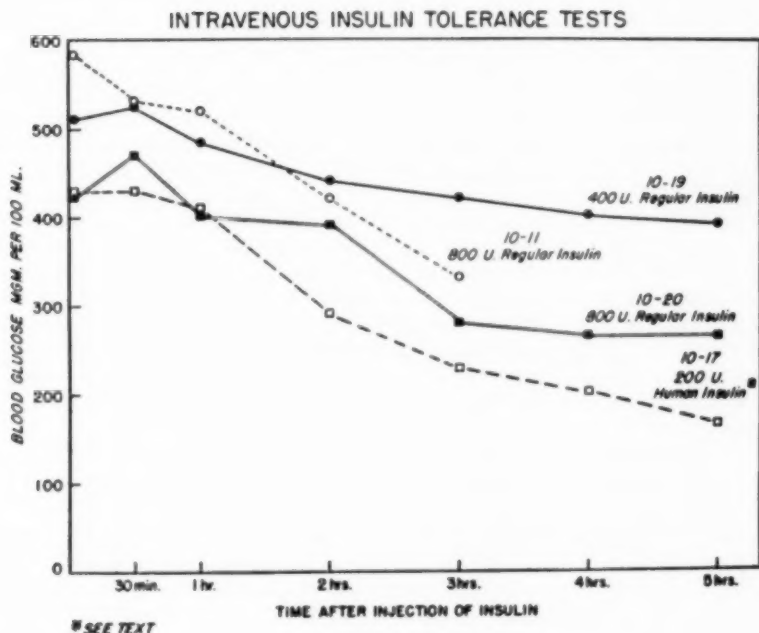


FIG. 3.

and human insulin were injected endermally in opposite forearms, with results as shown in figure 2A. For comparable doses of regular and human insulin the reactions were essentially equal. All the reactions elicited by the endermal injection of insulin had disappeared or faded markedly at the end of an hour. Skin tests were done several times and the results did not appear to be influenced by the length of time elapsing between the administration of insulin for the control of the diabetes and the skin tests.

Tests for skin-sensitizing antibody were done with serial dilutions of the patient's serum injected into the skin of a normal recipient (figure 2B). A normal serum was diluted and injected in the same manner. Twenty-four hours later, each site was injected endermally with a dilution of either regular or human insulin containing 4 units/ml. The loss in potency of the human insulin referred to above was not recognized at the time these tests were done, and the preparation of human insulin contained one half or one third this amount of active hormone. Examination 15 minutes later showed that the sites sensitized with the patient's serum reacted strongly and with about equal intensity to both kinds of insulin. In the sites sensitized with normal serum, little or no reaction occurred.

These tests established the presence of skin-sensitizing antibody in the patient's serum but failed to establish species specificity for this antibody. Although the patient's own skin reacted to the endermal injection of both commercial and human insulin, and his serum contained skin-sensitizing antibodies for each, yet

at no time during the period in which he received large doses of insulin did he show any evidence of a systemic allergic reaction.

Intravenous Insulin Tolerance Tests: Intravenous insulin tolerance tests were done using varying amounts of both regular (U 80letin, Lilly) and human insulin. The patient received no insulin in the 24 hour period prior to the tests. The results are given in table 1, and selected tests are shown graphically in figure 3.

In eight of the 11 intravenous tolerance tests there was either a slight hyperglycemic response within the first hour, or there was no change in the blood glucose level. As the first blood sugar was not obtained until 15 minutes or more after the insulin was injected, the transient rise in blood sugar which might be expected to follow the intravenous injection of large doses of insulin^{4,5} may have been missed. When a significant fall in blood sugar occurred, the fall was slow and was most marked between the second and the fourth hour. It is believed that the dose of 800 units, given on two occasions, is the largest single dose of insulin ever used in an intravenous tolerance test. Nevertheless, at no time did the blood sugar drop below 175 mg. per cent, nor was there clinical evidence of hypoglycemia.

Tests done with human insulin showed resistance to this as well as to regular insulin, but in less extreme degree (table 1 and figure 2). With the exception of the first test, in which the dose of insulin was relatively small and where the expected spontaneous fluctuations in blood sugar might overshadow the effect of the insulin, the fall in blood glucose per unit of regular insulin was approximately 0.2 mg./100 ml. In two of the three tests with human insulin, on the other hand, the fall in blood sugar ranged from 0.7 to 1.32 mg./100 ml. per unit, assuming no loss of potency in this preparation. As there was good reason to believe that this insulin had deteriorated during storage, as explained above, the patient's responsiveness to human insulin may have been much greater.

TABLE I
Intravenous Insulin Tolerance Tests with Regular and Human* Insulin

Date 1950	Type of Insulin	Units Injected	Blood Glucose mg./100 ml.								Change in Blood Glucose mg./100 ml. per Unit of Insulin	
			Fasting	Time in Hours after Injection of Insulin							After 2 Hours	After 5 Hours
				1/2	1	1	2	3	4	5		
8/29	Regular	50	390	400	405	375	345	—	—	—	-0.90	—
8/30	Human	50*	395	410	390	400	410	—	—	—	+0.30	—
9/28	Regular	150	350	—	400	380	320	300	—	—	-0.20	—
9/29	Regular	300	380	—	380	388	310	256	—	—	-0.23	—
10/3	Regular	400	390	—	430	360	290	280	—	—	-0.25	—
10/5	Human	100*	380	—	368	326	256	380	—	—	-1.24	—
10/10	Regular	600	268	—	256	224	200	210	—	—	-0.11	—
10/11	Regular	800	585	—	530	520	420	330	—	—	-0.20	—
10/17	Human	200*	430	—	430	410	290	228	200	165	-0.70	-1.32
10/19	Regular	400	512	—	524	484	440	400	390	390	-0.18	-0.33
10/20	Regular	800	426	—	470	400	390	280	264	264	-0.04	-0.22

* See text for description of this preparation.

TABLE II
Number of Mice Showing Hypoglycemic Symptoms in Tests with Serum
Obtained on September 14, 1950

Serum Dilution before Mixing with Insulin Solution	Commercial Insulin 1:100		Human Insulin* 1:40	
	Patient's Serum	Normal Serum	Patient's Serum	Normal Serum
1:2	0	5	2†	5
1:4	3†	5	3†	5
1:8	5†	5	—	—

* See text for discussion of the potency of this preparation.

† Onset of hypoglycemic symptoms delayed as compared with controls. Groups of five mice were injected with 0.5 c.c. of a mixture containing diluted serum and 0.033 u. of insulin.

Tests for Insulin-Neutralizing Activity in Serum: As shown in table 2, the patient's serum diluted 1:2 prevented hypoglycemic symptoms in starved mice receiving a mixture of the diluted serum and insulin intraabdominally, whereas a normal serum, to which glucose was added to equal the concentration in the patient's serum, failed to do so. Higher dilutions of serum decreased the incidence of hypoglycemic symptoms or delayed their appearance. The insulin-neutralizing activity of the serum was less pronounced when tested with human insulin. This difference may be explained by species specificity or by the inadvertent use of a higher dose of human insulin in these tests.

DISCUSSION

The development of antibody for insulin as one cause of insulin resistance appears to be well established. Reported instances of resistance to insulin associated with the presence in the serum of insulin-neutralizing activity now number 10.⁶ One of the patients did not have diabetes,⁷ and one other was responsive to human but resistant to commercial (beef and pork) insulin.⁸ The serum of this patient and one other⁹ appeared to protect mice from the hypoglycemic action of commercial but not human insulin. Finally, four of 24 rabbits injected with insulin incorporated in an adjuvant became insulin resistant without the development of diabetes, and in one of these animals resistance to human insulin was shown to be absent.⁵ In this instance, a procedure which is well known to provoke antibody formation gave rise to insulin resistance which was demonstrably species-specific. Although the antigenicity of insulin has been questioned,¹⁰ it is difficult to explain a species-specific resistance to insulin on any but an immunologic basis. Thus a sufficient amount and variety of evidence has accumulated to warrant the conclusion that the physiologically active hormone, insulin, is antigenic, though fortunately only feebly so. Since in resistance to insulin we are dealing with changes in the physiologic action of the hormone, immune or allergic reactions to such non-insulin substances as may be present in the available preparations may be disregarded. Such substances may indeed give rise to allergic reactions or to demonstrable antibodies, but these cannot logically be expected to alter the response to the hormone itself in any consistent manner.

The present case had a high degree of resistance to commercial insulin and a less marked degree of resistance to human insulin, and the patient's serum interfered with action of both insulins in mice.

The experiments with human insulin were complicated by the loss in potency of this preparation which had occurred during more than two years of storage. Crude assay in mice indicated that one-half or two-thirds of the activity of the hormone had been lost. If the assumption is granted that the patient's resistance to insulin was actually caused by a neutralizing antibody, hormonally inactive insulin present in the preparation might combine with antibody and thereby reduce the ability of the latter to interfere with the active hormone. If this occurred, the human insulin would then be more active both in the skin tests and in overcoming the patient's resistance than the recent assay would suggest. Evidence indicating that insulin inactivated by cysteine could still actively combine with antibody has been presented elsewhere.⁸

The absence of allergic reactions to the injection of large intravenous doses of insulin is interesting in view of the patient's skin sensitivity and the presence in the patient's blood of skin-sensitizing antibody. This is reminiscent of pollen-sensitive patients who have received injections of pollen extract for treatment of seasonal hayfever or asthma and have acquired a high degree of tolerance to such injections. This acquired tolerance has been attributed to the development of an antibody with characteristics differing from those of the skin-sensitizing antibody, and this new antibody supposedly combines preferentially with the pollen antigen so as to "neutralize" it and prevent it from reacting with skin-sensitizing antibody.^{11, 12} Neutralization of the allergen (insulin) may have taken place in a similar manner in the patient reported here, with the result that the patient was not only resistant to insulin but also protected against allergic reactions which might otherwise have occurred. The evidence as to whether skin-sensitizing antibody as seen in patients with pollenosis can combine with the antigen or allergen so as to neutralize it or modify it in any way is conflicting.^{13, 14, 15, 16} Of particular interest in this regard is the study of a skin-sensitizing antibody for diphtheria toxoid which neutralized toxin.¹⁷ Skin-sensitizing activity, but not the capacity to neutralize toxin, was abolished by heating the serum to 60° C.

We believe that an effort should always be made to ascertain as accurately as possible the insulin requirement of patients with insulin resistance. Otherwise, large but nevertheless ineffective doses of insulin may be given. Management of these cases outside the hospital is often difficult and is attended by the danger that the patient's resistance to insulin may suddenly decrease and the patient nevertheless continue to receive large doses of insulin. This appeared to be the cause of death in the patient reported here. The attempt to give enough insulin after discharge from the hospital to control the glycosuria was undoubtedly ill advised. Perhaps a fasting blood sugar level of over 200 mg./100 c.c. should be tolerated along with moderate glycosuria, provided the patient is able to maintain his weight and vigor.

The finding of hemochromatosis at autopsy was unexpected. The well-known occurrence of insulin resistance in patients with diabetes and hemochromatosis has not been explained. In view of the lack of deposition of iron-containing pigment in the islet tissue of the pancreas, and the relatively restricted

distribution of the pigment in other tissues, it is possible that neither the diabetes nor the resistance to insulin was related to the hemochromatosis. According to Sheldon,¹⁸ insulin resistance is by no means the rule in bronze diabetes, as 70 per cent of the cases responded well to treatment with ordinary therapeutic doses of insulin, and some cases showed a marked tendency to hypoglycemic shock.

SUMMARY

The clinical course of a patient with a high degree of resistance to insulin is described. Death apparently occurred directly or indirectly from a severe hypoglycemic reaction to insulin at a time when the patient's resistance was decreasing. Hemochromatosis, discovered at autopsy, did not appear to play a part in the patient's course.

A series of insulin tolerance tests indicated that resistance to human insulin was less marked than that to commercial insulin. The patient's blood contained an insulin antagonist, presumably an antibody, demonstrable in mice. The patient was sensitive by skin test to both commercial and human insulins, and the blood contained skin-sensitizing antibody for both.

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ISLET CELL TUMOR OF THE PANCREAS WITH SURGICAL CURE*

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THE following case is reported because it demonstrates vividly the ramifications and complications brought about by severe hyperinsulinism. It is also interesting in that the symptomatology masked the true diagnosis for almost two years and led to many widely varying avenues of preliminary investigation.

CASE REPORT

A 60 year old white printer gave a history of having been in excellent health all his life until the early part of 1949, when he would awaken in the morning in a "confused and foggy state." He stated that his mind would clear in one-half hour to one hour after breakfast. His past history and family history were noncontributory. During the next three to four months the patient's family noted that he was subject to "convulsions" early in the morning. These episodes were manifested by unconsciousness, tremors of the face and extremities, and clonic, thrusting motions of the arms and legs, but were not associated with a warning aura, nor was there tongue biting or incontinence. Mental confusion invariably followed these attacks, but the patient on emergence was unaware of what had happened. For the first half of 1949 these seizures occurred approximately once a month, and for the next six months about twice monthly. A local physician who was consulted diagnosed and treated the patient for epilepsy.

During 1950 the convulsive episodes took place at much more frequent intervals, occasionally occurring two to three times daily. Personality changes became evident to his family and friends, who noted that his mannerisms and behavior "had become silly." He frequently giggled to himself, acted childishly and, on occasion, indulged in unconcealed masturbation.

The first glucose tolerance study was made on November 30, 1950, and, although it showed a third hour blood sugar of only 56 mg. per 100 c.c. of blood, the neurologic and psychiatric manifestations predominated so markedly that the diagnosis of hyperinsulinism was not entertained at that time. (See table I.)

* Received for publication October 21, 1952.

From the Division of Internal Medicine and the Division of General Surgery of the Central Medical Group of Brooklyn.

On December 7 the patient was referred to a neuropsychiatrist, who felt that it was essential to rule out an organic intracranial lesion before concluding that the condition was primarily psychogenic in character. Accordingly, a neurosurgical investigation was conducted after the patient's hospital admission on January 22, 1951. At this time, x-ray study of the skull revealed a well demarcated, opaque lesion in the left frontotemporal region, ovoid in shape and measuring 8 cm. in its longest diameter. This finding was interpreted as an osteoma rather than as an intracranial lesion. Pneumoencephalography disclosed no displacement or deformity of the ventricular system. Spinal fluid study was within normal limits. An electroencephalogram showed evidence of a diffuse abnormality, maximal over the left temporal region. Because of this latter finding, it was felt that the bony lesion in the left temporal region should be removed and that burr holes should be made to determine whether a local lesion, such as a subdural hematoma, was present. The patient, however, would not consent to this procedure and was discharged from the hospital against advice.

During the first few months of 1951 his neurologic and psychiatric symptoms continued unabated. He developed a voracious appetite and gained 30 pounds, attaining a weight of 165 pounds. In April the patient experienced a sudden episode of pain in both arms which lasted through the night and was accompanied by severe interscapular pain the next day. He developed a feeling of fullness and pressure

TABLE I
Glucose Tolerance Studies Prior to Surgery
(Blood Sugar in Mg. per 100 c.c.)

Date	Specimens	Fasting	$\frac{1}{2}$ Hour	1 Hour	2 Hours	3 Hours	4 Hours	5 Hours
Nov. 30, 1951	Blood Urine	67 0	112 0	130 0	82 0	56 0		
Feb. 15, 1951	Blood Urine	70 0	160 0	115 trace	155 2 plus	60 2 plus	55 0	60 0
July 3, 1951	Blood Urine	63 0	128 0	226 0	262 4 plus			

in his chest but endured these symptoms and the continuation of his convulsive seizures for a week before calling upon his physician. A diagnosis of an acute coronary episode was considered. Electrocardiographic study exhibited evidence of an old anterior wall myocardial infarction. Subsequent studies failed to show an acute lesion. The patient recovered from this episode and returned to work within three weeks.

In the late spring of 1951 the patient's history and findings were reviewed thoroughly and a diagnosis of hyperinsulinism was made. He was admitted to the Jewish Hospital of Brooklyn on June 26, 1951, for further investigation and treatment.

Physical examination revealed an obese, well oriented, cooperative, alert man of 60 years who appeared younger than his chronologic age. His head and neck were essentially normal, with no evidence of cranial nerve lesions. The pupils reacted normally to light and accommodation, and the eyegrounds showed no abnormalities. The thyroid gland was not enlarged, nor were there enlarged cervical lymph nodes. His chest was clear and resonant throughout. The heart was not enlarged, and auscultation revealed regular sinus rhythm, sounds of good quality, and no murmurs. Blood pressure was 150/88 mm. Hg. The pulse rate was 94 per minute. His abdomen was soft and flat. No enlargement of the liver, spleen or kidneys was noted, nor were any masses palpable. The skin was clear and warm, and the hemic com-

ponent appeared to be good. All motor and sensory reflexes were tested and found to be within normal limits.

Laboratory investigation included a complete blood study, urinalysis, dilution and concentration test, blood sedimentation rate, blood urea nitrogen, non-protein nitrogen, sodium, potassium, cholesterol and esters, CO_2 combining power, amylase, 17-ketosteroids, prothrombin time, cephalin flocculation, thymol turbidity, icterus index, alkaline phosphatase, total proteins and albumin-globulin ratio. All of these tests revealed normal findings.

X-ray investigation revealed the following. Chest: No abnormality other than some calcification of the aortic arch. Stomach and duodenal studies: Normal. Flat plate of abdomen: Calculi in the right hypochondrium, believed to be gall stones. Skull: Evidence of an opaque lesion in the left frontotemporal region, as noted previously.

The patient displayed no mental aberrations and experienced no convulsive seizures during the first few days of hospital residence. He was placed upon a full diet but was confined to bed. On one or two occasions he complained of feeling faint, but this sensation disappeared when he was given additional food. Fasting blood specimens for glucose taken within the first 10 days of hospitalization showed the following levels: 39 mg. per cent, 42 mg. per cent, 182 mg. per cent and 65 mg. per cent. On the fifth day after admission the patient was placed on a complete starvation régime and late in the afternoon suffered one of his typical attacks, with loss of consciousness and clonic convulsions of the arms and legs. Blood, drawn while the patient was still unconscious, showed the glucose level to be 30 mg. per cent. Intravenous administration of glucose produced immediate relief from the seizure.

A surgical consultation was held to determine the advisability of an abdominal exploration for pancreatic tumor. This course was decided upon and on July 7 a laparotomy was performed. At operation, a well circumscribed, encapsulated firm mass, measuring approximately 1.5 cm. in diameter, was found in the tail of the pancreas near the hilum of the spleen. The mass was dissected free from the surrounding pancreatic tissue and excised. No other lesions were found on close inspection of the remainder of the gland. The liver was normal but the gallbladder contained several small calculi. There was no evidence of other intraperitoneal pathology.

The pathologic report on the excised specimen revealed the following: "Grossly, the specimen consists of an oval mass of tissue measuring 1.5 cm. in diameter. It is round, firm, encapsulated, pinkish white, and trabeculated. To the surface are attached fibrous and fatty tags. On cut section, several firm, white, smooth and glistening surfaces are seen. Three sections are taken for study. Microscopically, the tumor consists of round or irregularly polygonal cells, with round or ovoid deeply staining nuclei and pale basophilic cytoplasm. The cell outlines are indistinct for the most part. The tumor cells are in nests or in cords and strands and in places surround clear space. The stroma is abundant, dense and hyalinized. The cells definitely resemble those of the islands of Langerhans of the pancreas. In a few areas, cells tend to form small island structures. The other preparations show similar pictures. Tumor tissue is also seen, in places, within lymphatic spaces. This finding, according to some, may be found in benign islet cell tumors of the pancreas. Others might consider such tumors as malignant, at least histologically.

"Diagnosis: Islet cell tumor of the pancreas."

The patient did well postoperatively except for a mild wound infection which responded readily to antibiotic therapy. For the first four days after surgery he spilled large quantities of sugar in his urine, and the first glucose tolerance test after operation seemed to indicate a diabetic curve. (See table 2.) He was discharged from the hospital on July 29, the twenty-second postoperative day.

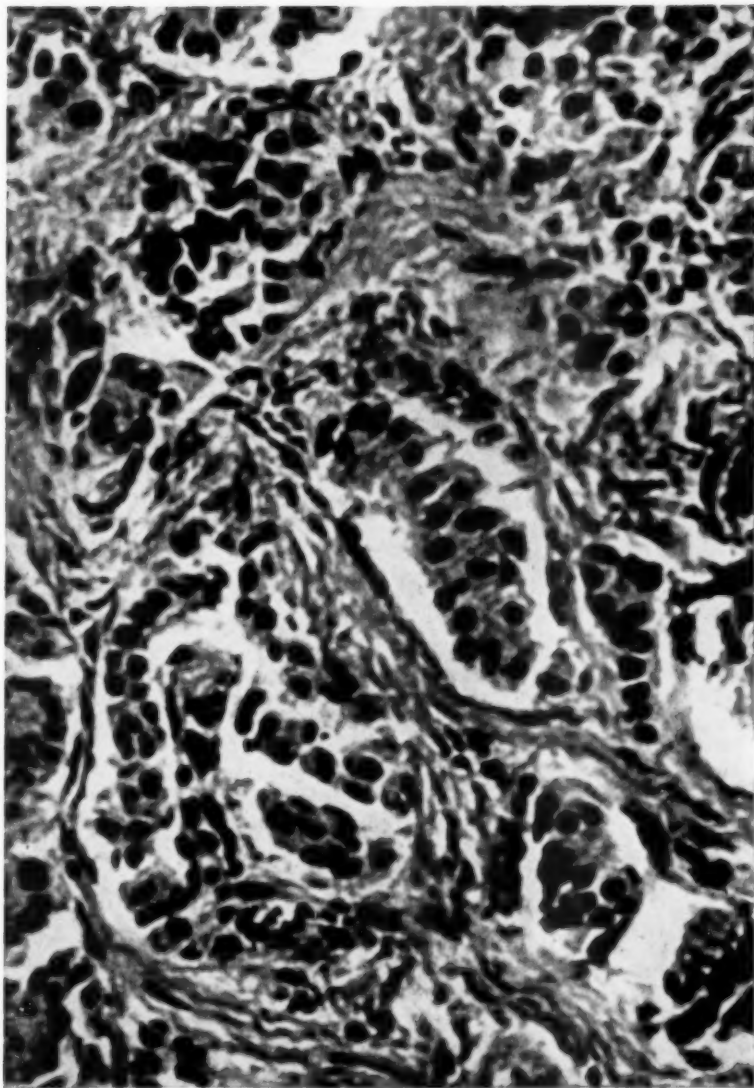


FIG. 1. Islet cell adenoma of pancreas. Note regularity of cells.

The patient has been completely free of his presenting symptoms since his discharge from the hospital. He disclaims any sensation of weakness, faintness or tremors when his stomach is empty. There have been no convulsive seizures and no disorientation or personality change, and a complete return to normal mental

and physical processes has taken place. The patient has no chest pain or other evidence of myocardial insufficiency. There has been no return of the marked desire for food, and the body weight has been at a level of 135 to 140 pounds during the year following surgery. Follow-up electrocardiograms show the old anterior wall in-

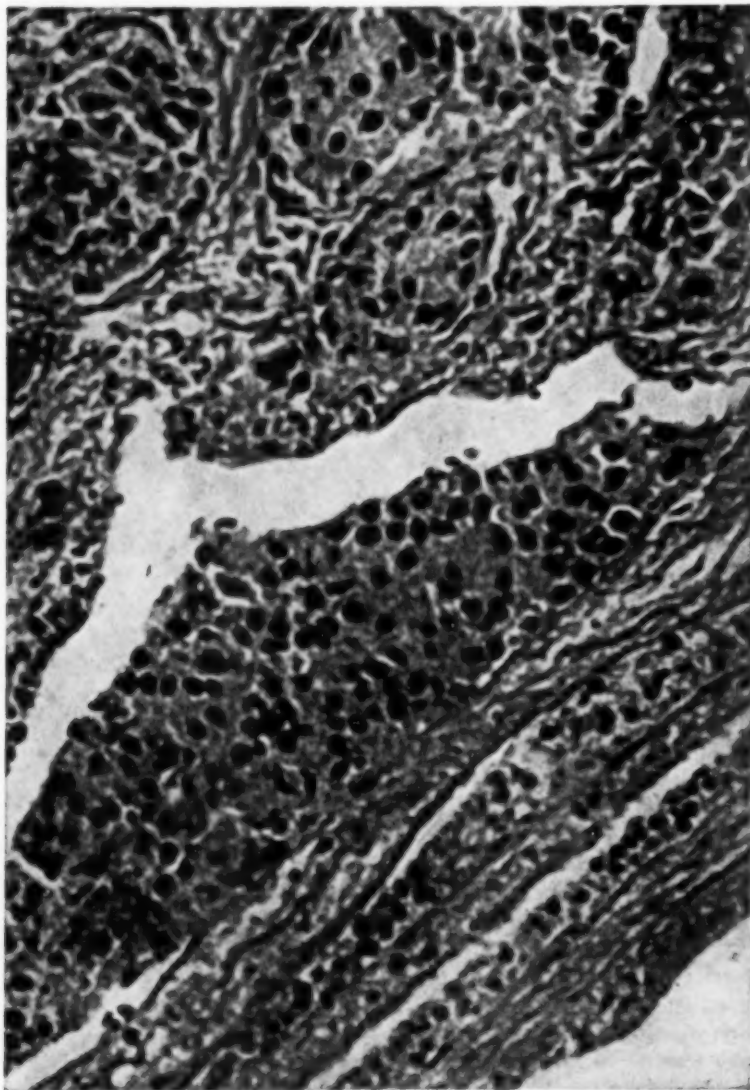


FIG. 2. Nests of tumor cells in vascular channel.

TABLE II
Glucose Tolerance Studies Following Surgery
(Blood Sugar in Mg. per 100 c.c.)

Date	Specimens	Fasting	½ Hour	1 Hour	2 Hours	3 Hours	4 Hours	5 Hours
July 24, 1951	Blood Urine	119 0	254 1 plus	220 1 plus	143 0	115 0	102 0	
Aug. 16, 1951	Blood Urine	130 0	222 0	215 0	215 0	222 0		
Nov. 15, 1951	Blood Urine	105 0	172 0	148 0	135 0	118 0	70 0	102 0
Feb. 26, 1952	Blood	80 0	90 0	96 0	118 0	100 0	92 0	73 0
July 17, 1952	Blood Urine	110 0	185 trace	202 trace	172 trace	85 trace	92 trace	110 0

fraction, with no new changes. A gastrointestinal x-ray series reveals a normal stomach and duodenum, with a normal duodenal sweep. A complete blood count is well within normal limits. A comparison of the glucose tolerance studies prior to operation with those done postoperatively indicates similar findings.

COMMENT

From the point of view of symptomatology this case is interesting in that the patient displayed so many of the untoward effects attributed to hyperinsulinism. It is quite unusual to find a patient (1) suffering from the hypoglycemic symptoms of ravenous hunger, faintness, tremors and convulsions; (2) showing personality changes with infantile regression, and, finally, (3) suffering a coronary thrombosis which was, in all likelihood, precipitated during a phase of excessive insulin secretion. The case is of further interest in that the neuropsychiatric manifestations were so pronounced that they overshadowed and obscured the real diagnosis for a long period of time.

Fineberg and Altschul,¹ in a recent communication, discussed mental changes and encephalopathy in hyperinsulinism. Their case reports were concerned with diabetic patients who had taken overdoses of insulin. One of their patients showed a reversal of personality changes and apparent organic cerebral damage which had been due to a post-hypoglycemic phase of hyperinsulin encephalopathy. They feel that the insufficiency of glucose in the cerebral tissue is sufficient cause for brain cell damage during repeated hypoglycemic states. The case reported shows many such hypoglycemic episodes, which could have been responsible for the brain changes described.

Although there have been some reports that S-T changes do not occur in patients receiving insulin shock therapy, in many instances S-T changes do occur after repeated episodes of hypoglycemic shock. Indeed, it has been stated that the lengthier the episode the less reversible the change. The irreversible nature of the electrocardiographic pattern in our case could be explained on this basis. It is plausible to assume that he had a small coronary closure during one of his

hypoglycemic convulsive episodes. Such a phenomenon has been seen frequently in diabetics during insulin shock.

It is of interest that the patient in this report developed mild diabetes mellitus following the removal of the pancreatic adenoma. This finding is not unusual and can be explained by the fact that the adenoma had appropriated almost the total responsibility for manufacturing insulin, and that the remainder of the islet cells spread throughout the gland had remained idle. Following removal of the actively secreting tumor, a latent period ensued during which the normal islet cells failed to secrete a sufficient quantity of insulin. The most recent blood sugar studies indicate that the islet cells have now resumed their normal function. It was important to differentiate the possibility of a functional hypoglycemia where the mechanism is exactly opposite to that which occurred in the case reported. In this type of hypoglycemia, the symptoms occur following the ingestion of food (particularly carbohydrates) which acts as a stimulant toward the production of an excessive amount of insulin.

The primary presenting symptoms of true hyperinsulinism are most commonly the result of the impact of sudden lowering of the blood glucose upon the higher centers of the central nervous system. This usually takes place when the blood sugar falls below 50 mg. per 100 c.c., or at a time when there has been no ingestion of food for several hours. All are acquainted with the symptom-picture which runs the gamut from mild headache, weakness and dizziness to mental confusion, muscle twitchings, convulsions, coma and, at times, death. Generally speaking, the longer the duration of the lowered blood glucose or the more frequent the attacks of hypoglycemia, the more severe are the resulting symptoms.

In dealing with patients presenting one or more of the above symptoms, there are several important pitfalls to avoid. Too often the diagnosis of hyperinsulinism is discarded when a single fasting blood sugar is found to be within the normal range. Also, it is often true that an isolated glucose tolerance test may fail to disclose hypoglycemia. Often, it is necessary that several glucose tolerance tests be taken before the diagnosis of true hyperinsulinism can be made. As a further aid in diagnosis, the effect of a 24 hour starvation régime is often of great value. Finally, prolonged hospital observation may be indicated. Failure to find definite intrapancreatic pathology should not eliminate the diagnosis completely, as islet cell tumors have occasionally been found in ectopic locations. By the same token, the removal of an islet cell tumor with recurrence of symptoms may indicate that another tumor has become active, or that one was left behind at operation. As we have seen in the case herein reported, mental symptoms may be so severe as to obscure the picture of hyperinsulinism. A previous diagnosis of epilepsy or psychosis should be reevaluated for the purpose of ruling out the presence of an islet cell tumor. Temporary improvement upon medication such as vitamins or barbiturates, or even hospitalization, does not negate the possibility of hyperinsulinism, since spontaneous remissions are known to occur in this condition.

This case emphasizes the importance of the statement made by Ryneerson² and others that the treatment of true, severe hyperinsulinism is a surgical exploration. Certainly, the benefits to be gained by extirpation of the functioning pancreatic adenoma far outweigh the dangers attendant upon an abdominal exploration.

SUMMARY AND CONCLUSIONS

1. A patient suffering from severe hyperinsulinism due to a functioning pancreatic adenoma is reported.
2. The patient presented marked hypoglycemic symptoms with convulsions, marked personality changes with infantile regression, and evidence of an old myocardial infarction.
3. The patient made a complete recovery following surgical removal of the adenoma.
4. Surgical exploration is advocated in all cases of pronounced hyperinsulinism, particularly in the absence of hypopituitarism or adrenal hypocorticism.

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ACUTE SUPPURATIVE CHOLECYSTITIS, WITH RUPTURE OF GALL-BLADDER AND LIVER ABSCESS FORMATION, DURING ADMINISTRATION OF CORTISONE*

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IT is by now well established that intercurrent infections become worse while the host—either human or lower animal—is receiving cortisone. Cases have been described in which the following entities have developed while the patients were receiving cortisone¹: thrombophlebitis, acne (to a greater extent than is usually ascribed to the masculinizing effect), abscess formation, tuberculosis, peritonitis, pulmonary fungus infections, bronchopneumonia, staphylococcal septicemia, empyema, disseminated fungus disease, suppurative pericarditis, sinusitis and renal abscess. Experimentally, mice are prone to develop spontaneous infections while on cortisone; they are also known to withstand infections poorly while on cortisone. It has become a commonplace procedure to investigate for peptic ulcer and tuberculosis prior to the institution of cortisone or ACTH therapy in view of the known tendency of these two diseases to flare up under steroid influence.

Cortisone masks the usual signs of acute inflammation—heat, redness, tenderness and pain. Organisms that are ordinarily harmless may become pathogenic with cortisone. Antibody formation is depressed. Inflammatory reactions are subdued and rendered inconspicuous with poor fibroblastic proliferation and lack of encapsulation.² The inflammatory reaction to injury should be followed under normal circumstances by a restoration of tissue integrity, but the interference with fibroblastic proliferation causes a delay in mesenchymal repair.³

The case to be presented is of interest for several reasons. First, it points up the imperative need to have patients receiving cortisone or ACTH under

* Received for publication November 15, 1952.
From the Jewish Hospital of Brooklyn, N. Y.

close and careful supervision. It demonstrates the complete lack of specificity of signs while cortisone is being administered, the signs evolving only after medication is stopped. *Escherichia coli* is very often found in cultures of gall-bladder bile even without clinical disease.⁶ However, cortisone has the potential power of making otherwise harmless organisms dangerously pathogenic. Combine this tendency with the presence of biliary calculi and cystic duct obstruction, the lack of fibroblastic or encapsulating activity, and the masking of clinical signs and symptoms, and it becomes readily apparent that a potentially catastrophic sequence is taking place.

In the case at hand the actual symptoms were present for about five days, yet localizing signs and symptoms did not appear until after four days of illness. At surgery there was a notable paucity of adhesions, in view of the presence of a ruptured hollow viscus, as well as an underlying pathologic process which must have existed for at least a week. Also, microscopic study of the gall-bladder wall failed to reveal the significant fibroblastic or lymphocytic activity which would be expected in an inflammatory process that had been present that long. It is possible that the aureomycin and penicillin, administered rather empirically prior to hospitalization, were significant factors in preventing the dissemination of the infection throughout the peritoneal cavity.

CASE REPORT

A 63 year old white male was first seen on October 13, 1952, for vague upper abdominal pains of several hours' duration, and a temperature of 100.4° F. The patient had had rheumatoid arthritis for 41 years and had been taking cortisone for the past four years. At the time of the present illness he was taking 62.5 mg. orally, with Butazolidin. Four years before the patient had had an attack of upper abdominal pain for which a gastrointestinal x-ray series was done and said to have been negative. The abdomen was soft and nontender. The patient was placed on antispasmodics and aureomycin, and the cortisone was discontinued. The next day he felt better, though there was still a low grade fever. On October 16 the pain increased in severity, although the abdomen was still soft. The next morning there was exquisite right upper quadrant tenderness, involuntary muscle spasm, and the suggestion of a globular mass in the gall-bladder area. That morning the patient was admitted to the Jewish Hospital of Brooklyn.

The laboratory findings were of no significance except for a white blood cell count of 17,200 per cubic millimeter, with 80 per cent polymorphonuclear leukocytes, and a sedimentation rate of 74 mm. per hour (Westergren). The patient was prepared with massive doses of antibiotics, intravenous fluids and whole blood, and operation was performed that evening by Dr. Edward Hirsch. The gall-bladder was found to be acutely inflamed, tense and dilated. There were only a few adhesive bands between the posterior wall of the viscus and the liver. There was a perforation of the posterior wall with a large abscess consisting of brownish pus embedded in the liver. The gall-bladder contained numerous calculi, with one large calculus in the ampullary region. Cholecystectomy was performed and the hepatic abscess was evacuated. Microscopic examination of the wall of the gall-bladder (by Dr. David M. Grayzel) revealed the mucosa to be denuded and the surface to be covered by dry fibrin and necrotic tissue. The subjacent layers were densely infiltrated with polymorphonuclear leukocytes, extravasated blood and markedly engorged blood vessels. The gall-bladder contents cultured out *E. coli*, which was found to be very sensitive to chloramphenicol (administered postoperatively). The postoperative course

was uneventful except for urinary retention, which disappeared after frequent catheterizations and the use of Urecholine and Prostigmine.

At the time of this writing (four weeks after the operation) the patient is well except for mild arthritic symptoms and very minute drainage from the lower pole of the operative incision.

SUMMARY

1. A case has been presented of rupture of a suppurative cholecystitis (with cholelithiasis) while the patient was receiving cortisone. A review of the literature fails to reveal the report of a similar occurrence.

2. The effects of cortisone and ACTH on infections and host response to infectious agents are reviewed.

3. While patients are receiving cortisone or ACTH, it is urged that very careful vigil be kept for the insidious manifestations of infectious processes, of both a medical and a surgical nature, in addition to making the usual checks on fluid and salt retention, hypokalemia, hypertension, hyperglycemia and glycosuria.

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LISTERIA MENINGITIS *

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THIS report concerns a patient with meningitis due to the organism *Listeria monocytogenes*. The case is of interest not only because of the rarity of this disease (only 41 cases having been reported in the literature^{1, 4-16}), but also because of the difficulty in establishing a diagnosis and because for a time the patient was thought to have tuberculous meningitis. The correct diagnosis was made only after therapy for the latter disease had been instituted. Moreover, two antimicrobial agents were successfully used in therapy.

CASE REPORT

The patient was a 41 year old white male farmer and truck-driver transferred from a Southwest Missouri hospital on September 21, 1951, complaining of headache, stiff neck and fever. Two weeks prior to admission the patient had developed left-

* Received for publication December 3, 1952.

From the Division of Infectious Diseases of the Department of Medicine, Washington University School of Medicine, and the Diagnostic Laboratories of Barnes Hospital, St. Louis, Missouri.

sided headache which gradually became generalized and was associated with fever, shaking chills, intermittent diplopia, dizziness and weakness. His local physician noted a severe pharyngitis and administered 400,000 units of penicillin daily for seven days. At this time the patient noted in his nose a furuncle which drained on pressure. One week prior to admission to Barnes Hospital the patient developed a stiff neck. He was admitted to another hospital, where two lumbar punctures were performed within a 48 hour period. The findings are noted in table 1 (September 17 and 19). The white blood count was 10,300. A chest x-ray showed miliary healed calcifications. Skull films were normal. The patient knew of no exposure to tuberculosis. There was no history of recent insect bites. System review was negative.

Upon physical examination the patient appeared acutely ill, with a temperature of 40.3° C., pulse 80, respirations 16, and a blood pressure of 160/55 mm. of Hg. He was drowsy but oriented. The skin was hot and dry, but without lesions. Positive physical findings included slight injection of the posterior pharynx, a few shotty inguinal lymph nodes, and a normal sized heart with a soft, grade II apical systolic

TABLE I
Spinal Fluid Findings

	9/17	9/19	9/21	9/22	9/23	9/24	9/25	9/26	9/28	10/1	10/8	10/16
Pressure			250	250	100		5	50	5	65	145	140
WBC	138	585	765	690	800	860	1,100	910	705	260	30	5
Lymphs	24	71	45	53	89	60	90	75		75		
Polys	114	29	55	47	11	40	10	25		25		
Sugar	26	54	24	13	0	0	27	22	38	45	42	53
Protein	126	200	154	228	198	187	155	156	118	124	77	75
Chloride			412	397	390		389		350	418	422	424
Culture	0		+	+	+	0	0	0	0	0	0	0
Streptomycin (mg. I.T.)			0	0	100	50	50	50	0	0	0	0

murmur. Neurologic examination revealed a fine tremor of the outstretched hands, normal optic discs, a stiff neck with pain on flexion, pain with straight raising of the legs, a left central facial paralysis, deviation of the uvula and of the tongue to the right, equal and active deep tendon reflexes bilaterally, and an equivocal Babinski reflex on the right.

Laboratory Data: Hemoglobin, 15.5 gm., red blood cells, 5.1 million; white blood cells, 24,700, of which 61 per cent were segmented forms, 16 per cent stab forms, 5 per cent juveniles, 18 per cent lymphocytes and 2 per cent monocytes. Urinalysis, stool examination and cardiolipin test were negative. Nose culture yielded coliform bacilli. Throat culture grew a few beta-hemolytic streptococci* and *Staphylococcus aureus*. Serum non-protein nitrogen, fasting sugar and electrolytes were normal. Histoplasmin and first strength P.P.D. skin tests were negative. Heterophil agglutination 10 days after admission was negative. Electrocardiogram eight days after admission was normal.

* Unfortunately the "beta-hemolytic streptococci" were discarded before the diagnosis of *Listeria* meningitis was made. That they may have been *Listeria* is a possibility.

Lumbar puncture on day of admission revealed a pleocytosis with lymphocytes and polymorphonuclear leukocytes, and a depressed sugar level. Values for this and subsequent spinal fluid examinations appear in table 1. Cultures of the first three specimens of spinal fluid revealed a gram-positive rod identified subsequently as *Listeria monocytogenes*. Attempts to demonstrate acid-fast bacilli by smears, culture and guinea pig inoculations were not successful.

Course in Hospital: Tuberculous or cryptococcal meningitis was considered the most likely diagnosis. However, because of the patient's high fever and leukocytosis, as well as his desperate appearance, chloramphenicol was administered. It was thought that this drug would provide a wide antibacterial coverage, would be absorbed well into the cerebrospinal fluid, and would not obscure further diagnostic investigation for tuberculosis and cryptococcosis. The patient remained oriented but febrile and in great distress. On the second day after his admission, due to his lack of response to chloramphenicol and following the third lumbar puncture, therapy for tuberculous meningitis was begun; it consisted of an initial dose of 100 mg. of streptomycin intrathecally, followed by 50 mg. injections daily for three days, 2 gm. of streptomycin intramuscularly daily, and 12 gm. of para-aminosalicylic acid orally per day. The patient's temperature fell below 38° C. for the first time on the next day, and he appeared clinically improved.

On the day following institution of streptomycin therapy, cultures of the first three spinal fluid specimens revealed a gram-positive bacillus which initially defied identification. Chloramphenicol, 3 gm. orally per day, was again instituted, and streptomycin and para-aminosalicylic acid were continued.

The patient's course was that of continued improvement. He was afebrile on the fifth hospital day and, except for a slight fever of 38.4° C. on the sixth hospital day, remained so throughout his hospital stay. The peripheral white blood cell count was 8,800 after seven days of therapy. The organism in the cerebrospinal fluid was finally identified as *Listeria monocytogenes*. All cultures taken subsequent to streptomycin therapy were sterile.

Intramuscular streptomycin was administered for seven days, chloramphenicol for 21 days. The patient's only complaints were evening headaches, which gradually subsided. The patient was observed for six days after therapy was discontinued, during which time he remained afebrile and asymptomatic. Two months after discharge the patient reported that he was feeling well except for the occurrence of frequent headaches and backaches.

CHARACTERISTICS OF THE ORGANISM

Cultures of three specimens of cerebrospinal fluid revealed small, smooth, beta-hemolytic colonies on blood agar and rough colonies on Sabouraud's medium at room temperature and after 48 hours. The organisms were gram-positive rods, approximately 0.5 micron in diameter and 1 to 3 microns in length. Growth occurred in thioglycollate broth. Six hour broth culture revealed organisms with a sluggish and tumbling motility. Lactose, mannose and xylose were not fermented, whereas dextrose and sucrose were fermented without gas formation. One milliliter of broth culture injected intraperitoneally into a mouse resulted in death in four hours. The organism was agglutinated with antimonocytogenes serum prepared by the late Dr. Julianelle. Broth culture placed on a rabbit's eye resulted in conjunctivitis.*

* The organism was identified as *L. monocytogenes*. The Communicable Disease Center of the Federal Security Agency at Chamblee, Georgia, concurred in identifying the organism as *L. monocytogenes*.

In vitro sensitivity studies by a tube dilution method resulted in growth in 100 mg. of sulfadiazine per 100 ml. and in 10 units of penicillin per milliliter. On the other hand, it was inhibited by 20 micrograms of chloramphenicol per milliliter but not by 5 micrograms per milliliter; and was inhibited by 5 micrograms of streptomycin per milliliter but not by 4 micrograms per milliliter. Growth was inhibited by a combination of streptomycin and chloramphenicol in a concentration of 0.5 microgram of each per milliliter.

COMMENT

Kaplan¹ reviewed 23 cases of *Listeria meningitis* appearing in the literature prior to 1945. An additional 18 cases⁴⁻¹⁰ have been reported from this country, the Netherlands, France, Scandinavia and Australia. A decade after Julianelle's writings,² Girard and Murray³ made an extensive study of the rôle of *Listeria* in human and animal disease. The transmission of the infection from animals to man has been strongly suggested.¹⁴ There is every reason to believe that these infections are more common than has been thought. The favorable reports concerning response to antimicrobial therapy increases the importance of recognizing such infections.

This patient did not present a picture typical of tuberculous meningitis. In addition to his rather alert appearance, the laboratory findings of a leukocytosis of 24,000, a spinal fluid sugar of 0, and the rapid subsidence of fever after the onset of therapy were disquieting features in the diagnosis.

The importance of obtaining an adequate number of cultures of spinal fluid before starting therapy in cases of suspected tuberculous meningitis is apparent and is perhaps the most striking lesson to be learned from this case. But since it is desirable to start streptomycin therapy as early as possible in tuberculous meningitis, it is often necessary to initiate treatment without actual demonstration of tubercle bacilli. Under these circumstances, we believe that the possibility of *Listeria meningitis* should be considered. If *Listeria* can be isolated, the prognosis is probably radically altered and the prolonged therapy for tuberculous meningitis can be avoided.

SUMMARY

A case of meningitis due to *Listeria monocytogenes* is reported. The patient was thought to have tuberculous meningitis, and therapy was begun before recovery of the organism was accomplished. The infection responded to streptomycin and chloramphenicol.

ACKNOWLEDGMENTS

The authors wish to acknowledge the kindness of Mr. William Moor, of the Department of Ophthalmology, in providing the antimonoctyogenes serum used in identifying the organism, and to acknowledge the aid of Dr. Carl G. Harford in the preparation of this manuscript.

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DEATH DUE TO WITHDRAWAL OF BARBITURATES*

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ALTHOUGH it is known that abrupt withdrawal of barbiturates from persons who have been chronically intoxicated with large amounts of these drugs may precipitate a serious abstinence syndrome,^{1, 2} a review of the American literature revealed no report in which death was attributed to abstinence from barbiturates. Three cases in which death was associated with withdrawal of barbiturates were found in the German literature. Two of these cases were complicated by the presence of organic disease (Buerger's disease with gangrene, and acute yellow atrophy of the liver with blood dyscrasia), so that abstinence from barbiturates could be regarded only as a contributing factor to death. In the third patient³ no complicating disease was found on physical examination, and death was in all probability due to withdrawal of barbiturates.

The usual course of the barbiturate abstinence syndrome may be described as follows: Upon abrupt withdrawal of barbiturates from individuals who have been ingesting 0.8 gm. or more daily of one of the potent barbiturates (secobarbital, pentobarbital, amobarbital), signs of barbiturate intoxication disappear in the

* Received for publication December 13, 1952.

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first 8-12 hours of abstinence, and, clinically, the patient seems to improve. Thereafter, increasing anxiety, insomnia, tremulousness, weakness, difficulty in making cardiovascular adjustments on standing, anorexia, nausea and vomiting appear. One or more convulsions of grand mal type usually occur during the second or third day of abstinence. Following the seizures, a psychosis characterized by confusion, disorientation in time and place, agitation, tremulousness, insomnia, delusions and visual and auditory hallucinations may supervene. The psychosis clinically resembles alcoholic delirium tremens, usually begins and is worse at night, and terminates abruptly with a critical sleep.

With respect to the incidence of the various signs and symptoms, Fraser and Isbell⁶ found that all of 19 patients who had been ingesting 0.8 to 2.2 gm. of amobarbital, secobarbital or pentobarbital chronically, exhibited anxiety, weakness, tremor, insomnia and paroxysmal bursts of abnormal waves in the electroencephalogram following abrupt withdrawal. Fifteen (or 80 per cent) had one to four convulsions; 12 (or 60 per cent) developed a delirium; four patients had seizures but no delirium; one patient had a delirium but no seizures, and three patients escaped both seizures and delirium, although they exhibited anxiety, weakness and electroencephalographic abnormalities. These data indicate that the type with a delirium without a seizure is the least common variant of the barbiturate abstinence syndrome.

In 17 of the 19 patients, symptoms disappeared within 10 to 14 days even though no treatment was given. The two remaining patients became so exhausted during the course of a protracted delirium that their lives were judged to be in danger; both were treated by rapid re intoxication with barbiturates, followed by gradual reduction^{2,4} of barbiturates, with satisfactory results.

The purpose of this communication is to present the clinical and pathologic findings in a case in which death was apparently due to the severe stress of the barbiturate abstinence syndrome superimposed on an already damaged cardiovascular system.

CASE REPORT

A white male physician, 49 years of age, was admitted to the USPHS Hospital, Lexington, Kentucky, at 11 p.m. on June 21, 1951. He gave a history of intermittent addiction to codeine since 1942. The maximal codeine intake had been 360 mg. daily, but this dose had been voluntarily reduced and no symptoms of abstinence from opiates were ever detected. He denied the use of barbiturates on admission but four days later, while psychotic, admitted using 0.3 to 0.5 gm. of secobarbital four times daily. When this information was obtained, the diagnosis of barbiturate abstinence syndrome was considered but could not be proved because of the unreliability of the patient's history. Subsequent to the patient's death a detailed history of secobarbital addiction was obtained from his wife. She stated that he had taken a high dose of barbiturates for eight months, and for the four months prior to admission had been ingesting 5.0 gm. (50 capsules) daily.

The patient had had the usual childhood diseases with no complications, and no adult diseases except appendicitis, with appendectomy in 1936. The only positive physical findings were obesity and a blood pressure of 170/90 mm. of Hg. The urinalysis, chest x-ray and blood Kahn were negative.

Course in Hospital: On admission the patient appeared to be in good physical condition; he had no signs of abstinence from codeine; he was cooperative in carrying out all admission procedures, talked coherently and wrote legibly. After 36 hours

of hospitalization he still showed no opiate abstinence signs or other symptoms and was transferred to a convalescent ward. One hour later he vomited, became very nervous and perspired profusely. He was dizzy and refused lunch, and was given 0.2 gm. of phenobarbital. At bedtime on the two previous days he had received 0.1 gm. of pentobarbital. On June 23, at 3:30 p.m. (40 hours after admission), he developed auditory and visual hallucinations and was transferred to a ward for acutely disturbed patients. At this time his oral temperature was 99° F.; pulse was 80 per minute; respiratory rate was 20 per minute, and blood pressure was 162/90 mm. of Hg. He was perspiring profusely, his pupils were somewhat dilated and he had a slight facial tremor. He was very nervous and tremulous but had no complaints of pain. He ate no lunch or dinner. During the night he did not sleep, was disoriented in place, and said there were a lot of boys and girls having a party in his room. On June 24 his condition was unchanged; he was given 0.1 gm. of Dilantin three times a day; he was oriented at intervals and confused at times. On June 25 these symptoms continued and the patient complained that his home town neighbors were watching him. He was given 128 mg. of phenobarbital at 8 p.m., and after 10:30 p.m. he slept fitfully. On June 26 the hallucinations continued and he was given 96 mg. of phenobarbital at 9 p.m. He was quite nervous and restless and did not go to sleep until 3 a.m. On June 27 he appeared improved and was transferred from the disturbed ward to the convalescent psychotic ward, but during the evening meal he again became disturbed and attacked a fellow patient and had to be separated from him. Later in the evening he attacked another patient, and then was locked in his room. At 10:40 p.m., while still locked in his room, he had hallucinations and claimed that someone was being killed and cut up by the attendant. At 12:45 a.m. on June 28 he was put in a wet pack for 45 minutes but continued to be restless and noisy. The pulse rate declined from 120 at 1:15 a.m. to 64 per minute at 1:30 a.m., shortly before the patient was removed from the wet pack. He was rubbed down with a towel and returned to his room. At 2:00 a.m. the blood pressure was 90/70 mm. of Hg; at 2:15 a.m. patient had gross tremors, and was jerking and twitching and stuporous; axillary temperature was 107° F.; pulse volume was poor and the rate was 120 per minute; the extremities were cold and cyanotic. At 2:30 a.m. cyanosis was general; there was incontinence of feces, and the twitching continued in all extremities; the pulse was rapid (rate, 120 to 146 per minute), weak and thready. The respiratory rate was 44 to 48 per minute. The blood pressure could not be obtained because of the convulsive movements; the skin was hot and dry; the pupils were round, regular and equal, and there was no nuchal rigidity. At 2:30 a.m. the patient was given 0.5 gm. of sodium amytal intravenously, following which his color and pulse improved and he became quieter. These effects wore off in about 45 minutes, but after repetition of the dose of sodium amytal he again improved temporarily. He was given 1 c.c. of ephedrine and 300,000 units of penicillin G intramuscularly, and 1,000 c.c. of 5 per cent glucose with 10 units of insulin intravenously. At 4:15 a.m. the jerking and twitching recurred, and 0.5 gm. of sodium amytal was given intramuscularly, but without any significant improvement. The axillary temperature continued at 107° F. The patient died at 4:37 a.m. on June 28, six days and six hours after admission to the hospital.

The clinical diagnoses (prior to obtaining a history of barbiturate addiction from the patient's wife) were essential hypertension, toxic psychosis of undetermined etiology, and fever of undetermined origin. The immediate cause of death, clinically, was attributed to "acute heart failure," probably resulting from abstinence from barbiturates.

Autopsy: Necropsy was performed six hours after death on the body which had been satisfactorily embalmed.

Gross examination was largely negative and supplied no completely adequate explanation of the cause of death. The *right lung* weighed 460 gm.; the *left lung*, 410 gm. Both lungs were fully crepitant throughout, except for a very small edematous area at each base. The *heart* weighed 500 gm. and was quite firm. The *pulmonary artery* was explored but no evidence of a pulmonary embolus was found. All the heart valve cusps were freely movable, of normal size and texture, and presented no evidence of sclerosis or incompetency. No coronary thrombi or areas of infarction were found. The left ventricular wall was greatly thickened, measuring 26 mm., but there was no dilatation of any heart chamber. The *liver* weighed 2,235 gm. and appeared enlarged with indistinct markings on section. *Genitourinary tract*, including kidneys, ureters and bladder, appeared grossly normal. *Spleen* was normal. *Adrenals*: The left adrenal, plus a small amount of fat, weighed 20 gm. Externally, both adrenal glands appeared normal, but on section the center of the medulla presented a cavity, probably resulting from postmortem autolysis. The medulla did not appear to be quite so distinctly brown as usual. The *gastrointestinal tract* was normal except for absence of the appendix and a few pericecal adhesions. The *brain* weighed 1,550 gm. The hemispheres were symmetrical and the brain was firm throughout. The gyri appeared to be somewhat flattened and the sulci moderately narrowed. The vessels at the base of the brain were normal in distribution and translucent, but there were a few atheromatous areas. An opening was made into the third ventricle and only a small amount of clear fluid exuded. Following fixation in formalin, sections at 1 cm. intervals revealed the brain tissue to be generally well preserved. The midline structures were not displaced; the ventricular system appeared approximately normal in size, with normal ependymal lining; there appeared to be some grayish mottling in some areas of the thalamus, substantia nigra, and possibly the lentiform nuclei. The substantia nigra was very prominent, both in the cerebral peduncles and in the upper midbrain, particularly on the right side. Serial sections made through the cerebellum, pons and medulla failed to reveal any significant gross abnormalities.

Microscopic Examination: The *myocardium* showed mild interstitial fibrosis. The pericardium and the endocardium appeared normal. An occasional small scar was seen in the myocardium. Sections from the *coronary arteries* showed atherosclerosis with considerable calcareous deposit. Sections of the *lungs* removed from the dependent portions showed edema but practically no inflammation. The *bronchioles* were not unusual. The *liver* showed marked fatty metamorphosis, but the remaining liver cells appeared quite normal. In the pancreas, the islands and acinar tissues presented no lesions. The *adrenal* cortical cells were pale. The *spleen* showed considerable sclerosis of the arterioles. The *kidneys* showed mild sclerosis of the medium sized arteries.

Brain: Microscopic sections were prepared from blocks removed from Rolandic cortices bilaterally, from the basal ganglia bilaterally, including the substantia nigra, and from the midbrain, pons, dentate nucleus and cerebellum. These were stained with hematoxylin (both alum and iron) and eosin, toluidin blue, phosphotungstic acid and hematoxylin, alizarin red and thionin, alizarin red alone and with Schiff's stain, the latter being a stain for mucin.

Frontal Cortex: Two blocks were stained as described. These revealed no marked changes in the leptomeninges. Throughout the cortex, patchy areas of nerve cell loss were observed. Many of the neurons appeared fairly normal, but Nissl substance was poorly preserved in most of these, although it could be seen distinctly in a few of the cells. The nuclei were eccentric in many of the nerve cells; others appeared swollen and distorted, and some showed disintegration. A few ghost forms were present. No intracellular vacuoles or abnormal globules were observed. Oc-

asionally neuronophagia and, rarely, satellitosis were seen, but there was no significant increase in glial or endothelial cells generally throughout the cortex. The smaller blood vessels showed a marked thickening of their walls with fibroblasts and endothelial cells.

Basal Ganglia: Foci of nerve cell degeneration and loss similar to those described in the frontal cortex were observed. The white matter in the internal capsule and elsewhere had a vacuolated appearance similar to that seen in cerebral edema. The ependyma of the third and lateral ventricles appeared normal.

Pons: These sections generally showed less severe degeneration of the nerve cells, while rare vacuoles were scattered through the section. Extracellular amorphous bodies, resembling corpora amylacea, were observed frequently toward the periphery of the section. No intracellular vacuoles or globules were observed. The neurons generally were slightly swollen, with some loss of Nissl substance, while a few possessed eccentric nuclei and were more distorted in outline. Satellitosis occurred rarely, and there was no generalized increase in glial or endothelial cells. The ependyma appeared normal.

Medulla, Adjacent Cerebellum and Dentate Nucleus: Numerous amyloid bodies were seen scattered at the periphery of the cerebellar folia; the cerebellar tissue generally had a vacuolated appearance. The Purkinje cells generally appeared swollen and showed diminution or loss of Nissl substance. A few cells were lost. Similar changes were observed in the cells of the dentate nucleus, although some of these appeared more distorted with eccentric nuclei. In some, no nuclei were demonstrable, but bluish granules were present in the cytoplasm in sections stained with thionin blue. There was some generalized increase in the number of endothelial cells in the cerebellar tissue, but no increase in glial cells was observed. Changes in the nerve cells and interstitial tissue of the medulla resembled those found in the pons. No intracellular globules or vacuoles were seen. The ependyma of the fourth ventricle appeared normal.

Comment: A special study was made in this case, in a search for mucoid bodies or globules scattered throughout the white matter or in the nerve cells themselves, as evidenced by the variety of stains used. No such collections were seen, and there was no evidence of degeneration of the basal ganglia grossly, as is sometimes described in barbiturate intoxication.

The *histopathologic diagnoses* were (a) *myocardial fibrosis*, mild; (b) *pulmonary edema*, mild; (c) *lobular pneumonia*, mild; (d) *fatty metamorphosis in liver*, marked; (e) *arteriosclerosis in spleen*; (f) *nephrosclerosis*, mild; (g) *atrophic changes in cortical cells of adrenals*; (h) *cerebral encephalopathy with diffuse neural degeneration*, and (i) *cerebral edema*.

DISCUSSION

That abstinence from barbiturates was responsible in large part for death in this case can scarcely be doubted. This opinion is supported by the confirmed history of ingestion of enormous amounts of secobarbital and by the clinical course, which was atypical only in that no convulsions were observed. What part the hypertension and the accompanying cardiovascular-renal pathology played in the fatal termination is difficult to assess. The nature and extent of the cardiovascular-renal damage were, however, hardly sufficient to account for the death alone. The same is true of the changes in the liver. The case of Meyer⁸ also developed an aggravated phase in the psychosis, a high fever and circulatory

collapse after being placed in a moist pack. His patient was a 30 year old female in good general health who had taken cyclobarbitol (Phanodorn) in excess for two years. At the time of admission she was taking 4 to 5 gm. daily. Barbiturates were abruptly withdrawn; two days later she was extremely weak and tremulous and had not slept for two nights. She was confused and hallucinating. She was given glucose and 4 gm. of Phanodorn by proctoclysis. On the third, fourth and fifth days hallucinations persisted, particularly at night, with intervals of relatively normal behavior. At 7 p.m. on the fifth day the temperature was 99.3° F. At 8:30 p.m. she was found in a severe delirium; she burrowed her head in the pillow and would not answer questions; she tossed about in bed and groped about with her hands. She was placed in a light moist pack in an effort to quiet her. After one-half hour she suddenly became pale and cyanotic and was gasping for breath, so she was immediately removed from the pack. The body temperature was now over 107.6° F. and the pulse was small and rapid, yet "well filled." The patient remained quiet until 12 p.m., when she suddenly died. The autopsy "revealed findings of a circulatory death with dilatation of the right heart, and congestion of the lungs." (No other autopsy observations were reported.)

Impairment of cardiovascular function (usually manifested by excessive tachycardia, sharp decline in both systolic and diastolic blood pressures, dizziness and faintness on standing, or even on sitting) is a characteristic feature of severe abstinence from barbiturates. It is quite probable that impairment in circulatory function played a significant rôle in the death of our patient and also that of Meyer. Probably warm baths and cold packs are contraindicated in abstinence from barbiturates, since the marked circulatory changes produced by these physiotherapeutic procedures might overwhelm an already functionally impaired cardiovascular system.

Death has also been observed following withdrawal of barbiturates from experimentally addicted dogs. Seevers and Tatum⁵ chronically intoxicated dogs with sodium barbital for four and one-half to 30 months. Some of their dogs died following convulsions after withdrawal of barbital. Fraser and Isbell⁶ observed one death following withdrawal of barbiturates from 17 chronically intoxicated dogs. The dog that died, a female that had been chronically intoxicated for 195 days with 47 mg./kg. of pentobarbital daily, showed no signs when 24 hours abstinent. When 35 and again when 36 hours abstinent, this dog had a grand mal convulsion. Following the seizures she showed weakness, extreme hyperactivity and abnormal behavior, and had a rectal temperature of 109.4° F. No pathologic changes of any significance (except for congestion of the thoracic and abdominal viscera) were found on gross and microscopic examination of the tissues, including the brain, of this animal.

Some of the histologic changes seen in the brain of our patient resemble some of those reported in experimental animals that were chronically intoxicated with barbiturates. The amyloid bodies are suggestive of those reported by McCrum et al.,⁷ or of the "mucinoid" bodies of Mott, Woodhouse and Pickworth.⁸ Loss of Nissl substance in Purkinje cells was also a feature in this case, as it was in the animals of Mott et al. None of the histopathologic changes reported in either animals or man can be regarded as being specific for chronic barbiturate intoxication, since they occur in other conditions. Furthermore, the relation of

pathologic changes in animals to withdrawal of barbiturates is obscure, since none of the reported studies was designed to observe the clinical picture and pathology of withdrawal per se. It is noteworthy that most patients chronically intoxicated with barbiturates recover completely within two weeks (as far as can be judged by clinical means) following withdrawal of the drugs. This fact suggests that, if chronic barbiturate intoxication does produce histopathologic changes, the changes are usually either reversible or not sufficiently extensive to produce gross impairment of function.

The occurrence of this death points up the opinion previously ventured,⁹ that abrupt withdrawal of barbiturates from chronically intoxicated persons is very dangerous and generally contraindicated. Withdrawal in this case was accidental and due to the patient's concealment of his enormous barbiturate intake from the physicians who were attempting to treat him. Had the diagnosis been made in time, proper treatment would have consisted of parenteral administration of barbiturates in sufficient quantity to induce eight to 12 hours of unbroken sleep, followed by regular oral doses of amounts of barbiturates sufficient to maintain a definite, continuous, moderate degree of intoxication. After several days on this régime, dosage of barbiturates should have been reduced cautiously (no more than 0.1 gm. daily) until withdrawal was completed.

SUMMARY

The clinical course and gross and microscopic pathology of a patient who died during the course of the barbiturate abstinence syndrome is presented.

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DIFFUSE INTERSTITIAL PULMONARY FIBROSIS CAMOUFLAGED BY HYPERMETABOLISM AND CARDIAC FAILURE: ANTEMORTEM DIAGNOSIS WITH BIOPSY AND CATHETERIZATION STUDIES*

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DIFFUSE interstitial fibrosis of the lungs, first described in 1944 by Hamman and Rich,¹ is a rare condition the diagnosis of which is established after death and only after careful microscopic studies.¹⁻¹² It is the purpose of this report to present a case of diffuse interstitial fibrosis of the lungs that was correctly diagnosed before death by means of cardiac catheterization and lung biopsy studies. The report is of additional interest because of several unusual features. First, the patient demonstrated early in the course of the illness a hypermetabolic state that was erroneously interpreted and treated as hyperthyroidism. Later he developed heart failure, the symptoms of which dominated the clinical picture and overshadowed the underlying pulmonary disorder. Finally, cortisone therapy was instituted. This is the first documented instance of diffuse interstitial pulmonary fibrosis in which it was possible to study microscopically the effects of this drug before and after therapy.

CASE REPORT

A single white 36 year old postman was referred to one of us (J. J. S.) on November 27, 1951, for a cardiac consultation because of increasing shortness of breath and nervousness of 10 months' duration. Approximately three months prior to his present complaints he had developed a dry cough which was diagnosed as a "viral bronchitis" and was treated with penicillin and aureomycin. The cough, however, persisted. He was able to carry on his work as a postman until the progression of dyspnea and nervousness, which necessitated a leave of absence from his work. He became discouraged, irritable and tremulous. Intolerance to heat was observed. A basal metabolic study in June, 1951, revealed a value of plus 49 per cent. A course of propylthiouracil was prescribed, but no improvement was noted.

The only significant past history was pneumonia in infancy. There was a long history of obesity since childhood; in 1940 he was rejected from the armed services because of a diagnosis of Froehlich's syndrome. The patient was born on Staten Island. As far as could be ascertained, he had never been exposed to any occupational respiratory hazard.

On physical examination the patient was well nourished and presented a Froehlich-type habitus. He was obviously anxious and slightly dyspneic at rest. There were suggestive cyanosis of the nailbeds and early clubbing of the fingers (figure 4). The lungs were normal to auscultation except that expiration was slightly prolonged; no adventitious sounds were heard. The apical cardiac impulse was not palpable. There was a grade II systolic murmur inside the apical area. P₂ was strikingly accentuated and louder than A₂. The blood pressure measured 150 mm. of mercury

* Received for publication November 21, 1952.

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systolic and 100 mm. diastolic. The pulse rate was 96 and regular. The abdomen was obese; the liver edge was nontender and was palpable one fingerbreadth below the right costal margin. The thyroid gland was not enlarged. There was no exophthalmos. The neck veins were not engorged. There was no pretibial edema. Ophthalmoscopic examination disclosed fullness of the veins; no exudate was seen. The discs were normal.

A roentgenogram of the chest disclosed increased markings at the lung bases. The cardiac silhouette presented no characteristic configuration (figure 1). On fluoroscopic study it was thought that there was some fullness and roundness of the inflow and outflow tract of the left ventricle. The electrocardiogram (figure 3) showed peaked P waves in Leads I and II, slightly depressed RS-T segment in Lead III and AVF; inversion of the T waves in Leads V₁ to V₄; a large R wave in V₁, and a relatively small R wave in Leads V₅, V₆ and V₆.

The red blood cell count was 5,600,000 per cubic millimeter, with a hemoglobin concentration of 17.8 gm. per 100 c.c. The hematocrit was 59 per cent. The white blood cell count was 13,800 per cubic millimeter, with 73 per cent polymorphonuclears, 23 per cent lymphocytes, 3 per cent monocytes and 1 per cent eosinophils. The platelet count was 573,000 per cubic millimeter. A urinalysis was normal. A blood Kahn serologic test for syphilis was negative.

On February 11, 1952, the patient was referred to Montefiore Hospital, New York City, for special studies. Physical examination at this time revealed no additional findings of significance. The venous pressure measured 80 mm. of water; the Decholin circulation time was 13 seconds. A glucose tolerance test disclosed a normal pattern. A bone marrow study was compatible with secondary polycythemia. The serum sodium determination was 139 mEq. per liter. The blood cholesterol was 250 mg. per 100 c.c. A sputum culture for fungi was negative. One sputum examination for acid-fast bacilli was also negative. An x-ray study of the skull disclosed no abnormalities. A tracer dose of I¹³¹ demonstrated a 24 per cent uptake in 24 hours, constituting a euthyroid pattern.

Pulmonary function and cardiac catheterization studies disclosed the following*:

PULMONARY VALUES

Vital capacity	2,220 c.c.
Maximal breathing capacity	157 L. per minute.
Oxygen uptake at rest	301 c.c. per minute equal 161 c.c. per minute per square meter of body surface.
Minute volume at rest	10.33 L. per minute equal 5.49 L. per minute per square meter of body surface.
Oxygen uptake with exercise	532 c.c. per minute equal 283 c.c. per minute per square meter of body surface.
Minute volume with exercise	20.30 L. per minute equal 10.8 L. per minute per square meter of body surface.
Cardiac output at rest	7.24 L. per minute equal 3.85 L. per minute per square meter of body surface.
Cardiac output with exercise	9.05 L. per minute equal 4.81 L. per minute per square meter of body surface.
Arterial oxygen saturation at rest	90.4 per cent.
Arterial oxygen saturation with exercise	86.6 per cent.

* These studies were performed by the Pulmonary Division (Dr. Abraham S. Buchberg) and the Cardiac Catheterization Team, Montefiore Hospital, New York City.

CATHETERIZATION VALUES

Site	Pressure (mm.)	Mean (mm.)
Left pulmonary artery	48/23	30
Right pulmonary artery	48/25	37
Right pulmonary capillary	—	8
Left brachial artery	125/77	102
Right ventricular	40-50/0	20
Right auricular	—	0
Right pulmonary artery		
½ minute of exercise	77/43	53
1 minute exercise	92/50	60
1½ minutes exercise	76/43	54 dizziness
6 minutes after exercise	48/23	27 cyanosis

Summary of Studies: The ventilatory mechanism discloses normal values. The maximal breathing capacity is above average. The cardiac output is increased. There is arterial underoxygenation. The pressure in the right ventricle and pulmonary arteries is elevated.

On March 1, 1952 through an incision at the fourth right intercostal space (figure 4) a biopsy of lung tissue was obtained. On microscopic examination this demonstrated interstitial fibrosis of the pulmonary parenchyma. There was extensive invasion of the alveolar septa by fibrous tissue and phagocytes. The alveolar lumina were reduced or obliterated; proliferation of the alveolar cells was striking. No primary vascular disease was noted (figure 5).

The patient was discharged from Montefiore Hospital on April 2 with no appreciable change in his condition. He had been afebrile throughout his hospital stay.

On May 28, 1952 the patient was started on a course of cortisone, and this was continued for two months. During the first three weeks the dose varied from 200 to 250 mg. of oral Cortone, and toward the end of his course he received a daily dose of 75 mg. Massive doses of aureomycin and penicillin were also prescribed concomitantly. During the first two weeks of treatment there was moderate improvement; dyspnea seemed less and there was a feeling of euphoria. This improvement, however, was only temporary. He gradually developed a weight gain accompanied by increasing dyspnea. Digitalis and frequent mercurials were now administered. His clinical course was steadily downward, characterized by right sided heart failure. There were engorgement of his neck veins, pitting edema of his lower extremities, liver enlargement and intense cyanosis to his lips and mucous membranes. There was a blowing systolic murmur over the apical region of his heart, and the accentuated pulmonic second sound previously noted was now even more exaggerated. The heart rate averaged 110 per minute and the rhythm was constantly sinus tachycardia. Follow-up roentgenograms of the chest (figure 2) disclosed an increase in the size of the transverse diameter of the heart, with prominent hilar and lung markings, especially at the bases. These findings were interpreted to be consistent with congestive heart failure.

On September 15, 1952 the patient suddenly complained of severe generalized abdominal pain, associated with some vomiting. He was admitted to the Staten Island Hospital in a critical state. He died three days later in heart failure complicated by an obscure abdominal condition.

Necropsy Findings: The lungs completely filled the thoracic cavity. The left pleural cavity was obliterated because of dense fibrous adhesions. A few adhesions were also present in the right pleural cavity posteriorly between the lung and diaphragm. Both lungs were dense, noncrepitant and inelastic. The right lung weighed 750 gm. and the left 800 gm. The cut surface of each lung was dry and brownish red, and demonstrated a honeycombed pattern (figure 6). An occasional circumscribed,

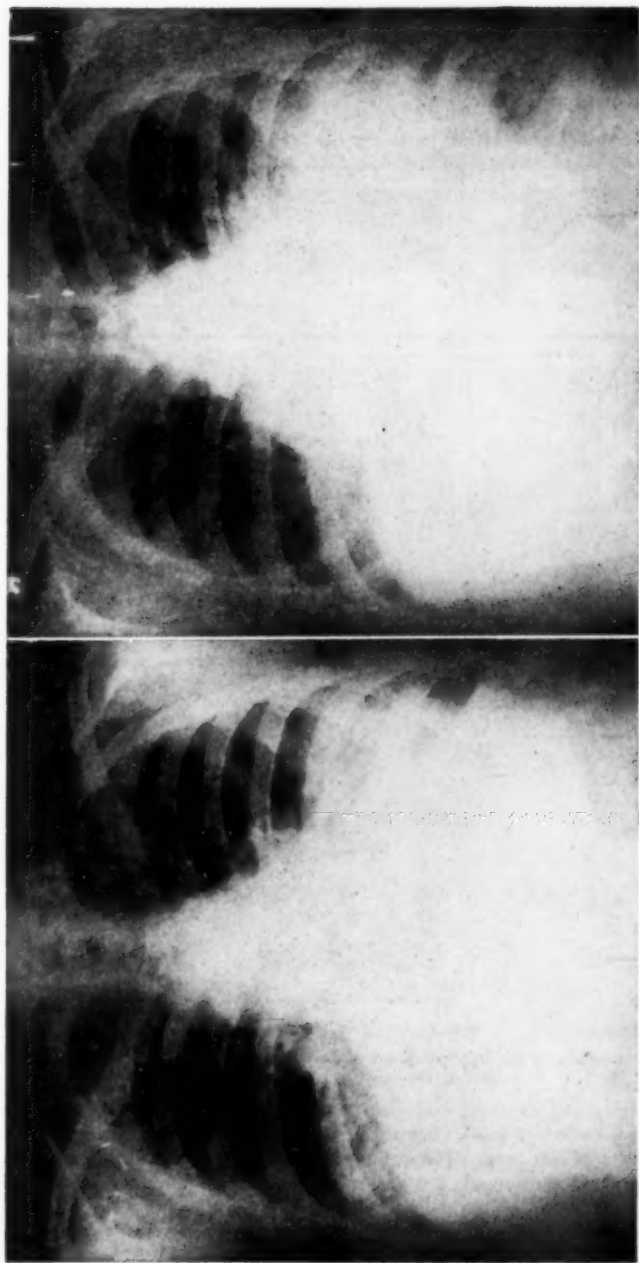


FIG. 1. Roentgenogram of the chest taken in October, 1951. Note peribronchial thickening of both bases.

FIG. 2. Roentgenogram of the chest taken in September, 1952. Note enlargement of heart and congestion of lungs.

stony hard deposit measuring less than 2 mm. was interspersed in the lung parenchyma (figure 6). No exudate was expressed from the cut surface. The mucosae of the trachea and major bronchi were normal. The intimal surface of the pulmonary artery and its branches was smooth. Microscopic sections throughout most of the lung showed an invasive connective tissue process resulting in a widening and

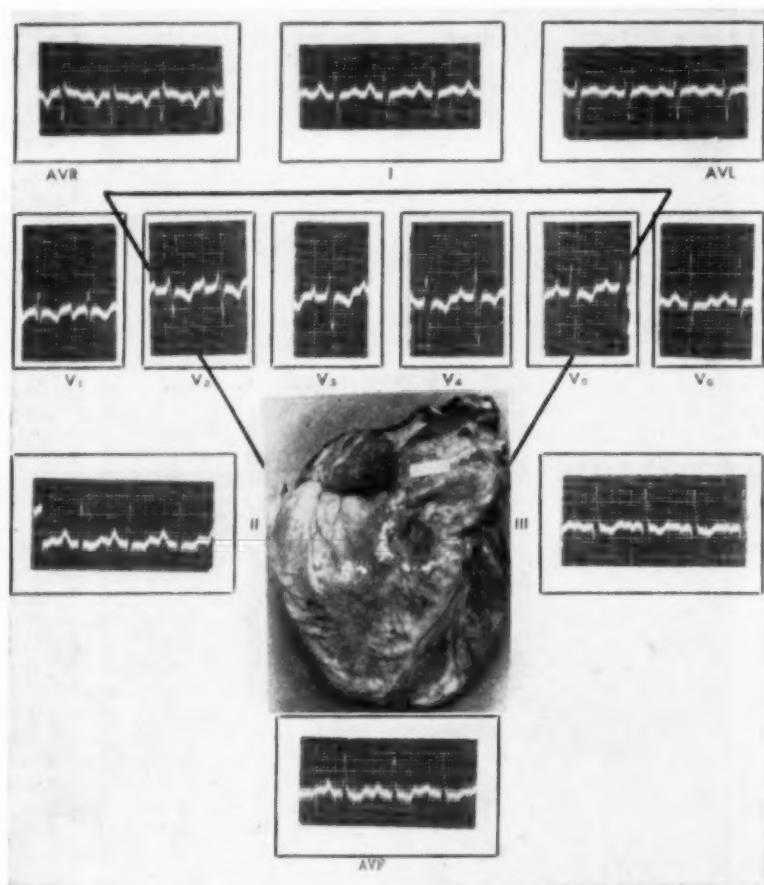


FIG. 3. Demonstrating the hypertrophied right ventricle and the cor pulmonale pattern of the electrocardiogram.

thickening of the alveolar septa (figure 7). This was particularly marked in the subpleural portions of the lung. The cellularity of this connective tissue process was low; occasional areas showed nonspecific mononuclear infiltration. An occasional alveolus contained a collection of macrophages, some of which appeared to be hemosiderin-laden heart failure cells. There was no epithelialization of the alveoli. Inter-

spersed here and there were isolated areas of emphysema. The smaller arteries and arterioles showed in some sections irregularities in the thickness of their walls.

The heart weighed 550 gm. The right auricle was distended, and an enormous right ventricle occupied most of the frontal plane rotating the left ventricle posteriorly (figure 3). It was estimated that the right heart was enlarged to twice its normal capacity. The wall of the right ventricle measured 0.9 cm. in thickness. The heart valves were normal. The aorta showed no evidence of atherosclerosis.



FIG. 4. Photograph demonstrating clubbing of the fingers. Inset shows site of lung biopsy. Note hypertrophied breasts.

The liver weighed 1,425 gm. A brownish gray area of infarction measuring 12 cm. in diameter projected through the dome. The portal vein was thrombosed and contained a mottled, grayish red, elastic thrombus with early adhesions in the intrahepatic branches. Propagation of this thrombus was present in the splenic vein in its terminal portion before entering the portal vein, and in the superior mesenteric vein.

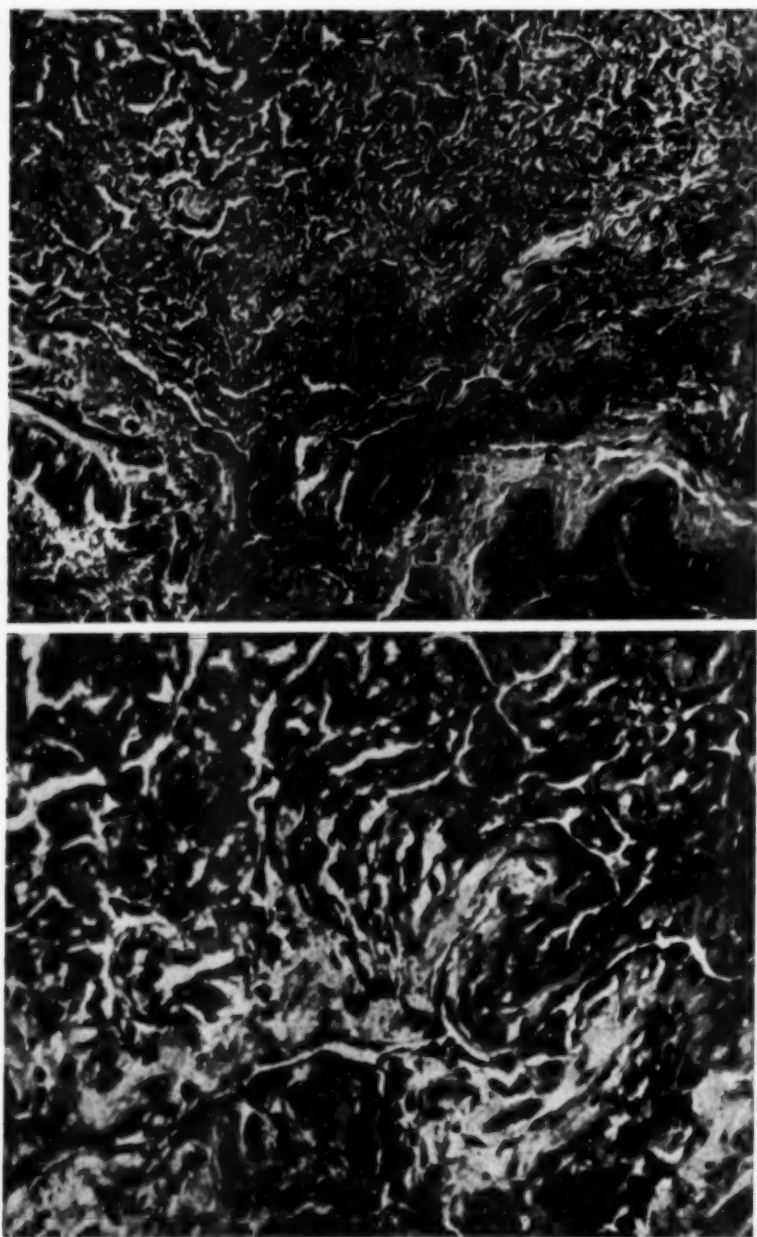


FIG. 5. Section of lung biopsy tissue. Note extensive proliferation of fibrous tissue. Below, high magnification demonstrating proliferation of cellular elements in the alveolar septa. Hematoxylin and eosin stain; $\times 175$.

The ileum, extending for a distance of approximately four feet, was gangrenous and presented a bluish black and swollen appearance (figure 6).

The thyroid gland was not unusual. The acini were normal and contained normal appearing colloid.

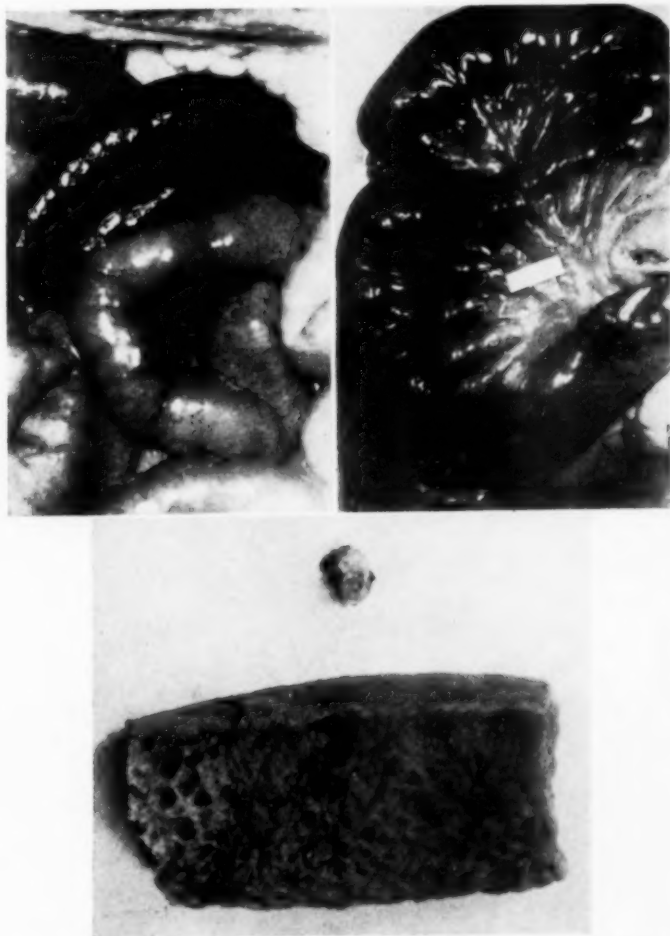


FIG. 6. Autopsy findings demonstrating a gangrenous loop of intestine and a section of lung tissue. Note honeycombed appearance of lung with a minute mineral particle removed from the subpleural surface.

The final anatomic diagnoses were: (1) Diffuse interstitial pulmonary fibrosis with patchy pulmonary emphysema, adhesive pleuritis, and occasional, minute subpleural mineral deposits. (2) Cor pulmonale. (3) Thrombosis of the portal, splenic and superior mesenteric veins. (4) Infarction of the liver. (5) Infarction with gangrene of small intestine.

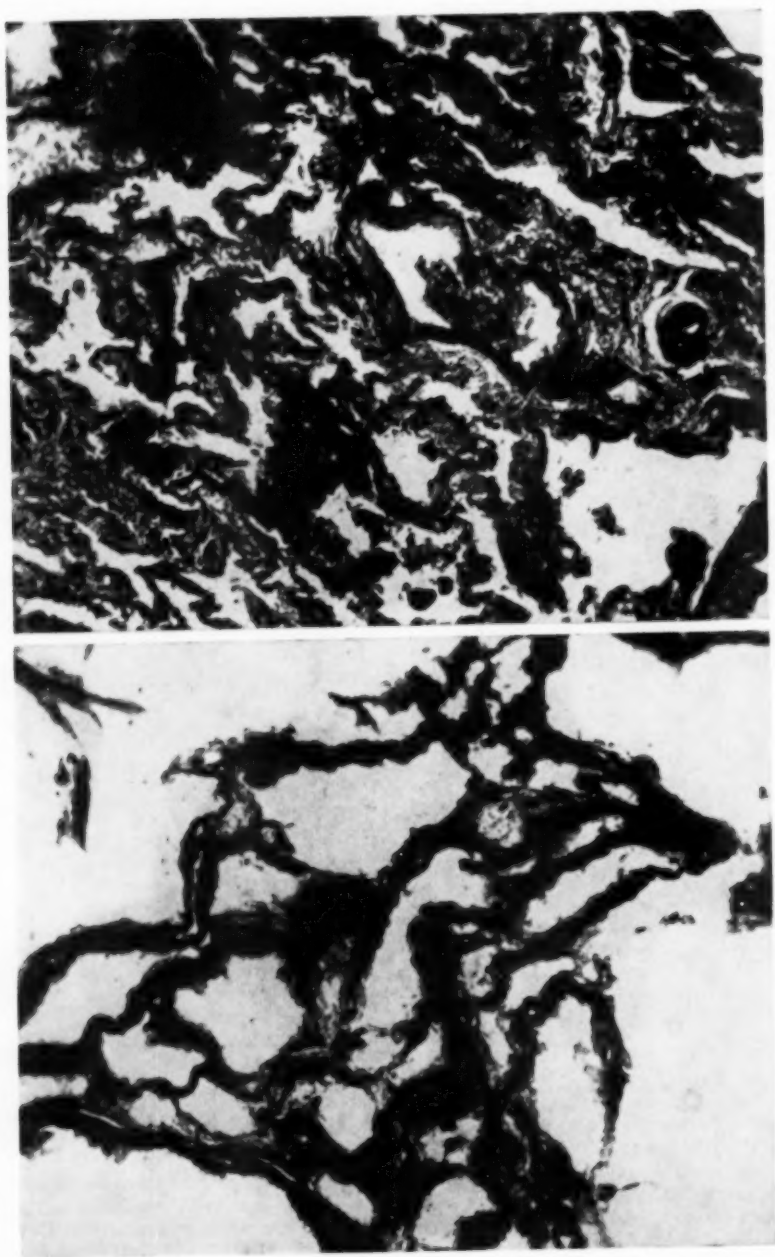


FIG. 7. Representative microscopic sections of lung tissue from autopsy. Note extensive proliferation of connective tissue between the alveolar walls.

DISCUSSION

Fibrosis of the lungs, in one form or another, occurs in a wide variety of clinical conditions. It is often a surprise finding at autopsy and in many instances is of no clinical significance. The degree and extent of fibrosis observed pathologically do not necessarily correlate with the clinical findings. With the advent of pulmonary functional and cardiac catheterization studies, many of the discrepancies between the pathologic and clinical findings are now being resolved. As Spain pointed out,¹³ the pattern of fibrosis determines to a large extent the type of functional disability. Diffuse interstitial pulmonary fibrosis has now been observed in at least 17 patients and a characteristic chain of symptoms has been noted.¹⁻¹²

The clinical findings of the previously reported cases have been abstracted by Rubin et al.¹¹ and reviewed by Callahan et al.¹² The presenting symptoms in the majority of instances have been cough, dyspnea, weakness, hemoptysis, cyanosis and fever. On physical examination the findings are usually minimal and not in proportion to the disabling complaints. It should be pointed out that although the disease is primarily one involving the lungs, the pulmonary features of diffuse interstitial pulmonary fibrosis may be entirely obscured by the effects of the disease process on the heart and circulation. Clinically, for example, the condition may manifest itself solely as one of heart failure. In fact, there are few pulmonary conditions in which cardiac decompensation is so striking and constant. Early in the course of the disease radiologic evidence of interstitial pulmonary fibrosis is frequently scanty or missing. When heart failure sets in, congestion of the lungs may obscure the primary pulmonary condition. In their original description of interstitial pulmonary fibrosis Hamman and Rich¹ emphasized the acute nature of the illness and observed the development of heart failure in all their patients. In subsequent reports of this condition cardiac symptoms have been the rule, with right-sided heart failure a prominent terminal feature.²⁻¹²

The mechanism of heart failure in diffuse interstitial pulmonary fibrosis stems from several factors, the most important of which is anoxia. This is understandable when one examines the microscopic section of the lungs of this condition (figures 5 to 7). The enormous connective tissue proliferation in the alveolar septa obviously alters the relationship of the pulmonary capillaries to the alveolar lumen. In careful physiologic studies Cournand and his co-workers¹⁴ have demonstrated in similar conditions an interference with the diffusion capacity of the lungs for oxygen. The term "alveolar capillary block" was proposed for such a state. Unfortunately, detailed ventilation-perfusion studies as described by Riley and his co-workers¹⁵⁻¹⁶ were not performed on our patient, so that a precise quantitative expression of the permeability of the alveolar-capillary interspace is not available. Nevertheless, our patient demonstrated a normal maximal breathing capacity, indicating normal ventilatory function and a low saturation of the arterial oxygen at rest. This paradoxical finding of a normal ventilatory mechanism associated with arterial underoxygenation is a feature of the alveolar-capillary block syndrome.

In addition to an impairment of oxygen diffusion, the fibrotic process encroaches on the pulmonary vascular bed, thereby reducing its capacity and thus increasing the resistance in the pulmonary circulation. Consequently the pressure

at the pulmonary artery rises; the right ventricle dilates and hypertrophies, and eventually intractable right heart failure develops—the classic picture of *cor pulmonale*.¹⁷ There is also a rise in the cardiac output, but the explanation for the high cardiac output is not clear; it is not necessarily on a hypervolemic basis.¹⁸ Nevertheless, a significant increase in red blood cell volume may occur in diffuse interstitial pulmonary fibrosis as a result of the anoxic stimulus to the bone marrow. Polycythemia is a common finding in the late stages and undoubtedly contributes to the heart failure and tendency toward thromboses.

The elevated metabolism found in our patient is interesting. There are a great number of clinical conditions accompanied by hypermetabolism that may be confused with hyperthyroidism.¹⁹ It is difficult to be certain of the accuracy of the basal metabolic reading in our patient because of the presence of anxiety, dyspnea and hyperventilation. In a recent study of patients suffering from pulmonary disease with impairment of their alveolar-capillary diffusion, in those patients without cardiac failure¹⁴ a higher than normal oxygen intake associated with an increase in cardiac output was observed. According to Cournand and his co-workers,¹⁴ this increased metabolism that is frequently observed may be on the basis of a "disseminated and active pathologic process." Metabolic studies in diffuse interstitial pulmonary fibrosis have not been reported, but it is conceivable, in view of the multiplicity of factors, that an elevated metabolism will be commonly observed in this condition. In our patient it was one of the earliest manifestations that directed the patient to the physician, and was erroneously interpreted and treated as hyperthyroidism.

Encouraging results with cortisone therapy have been observed in sarcoidosis and berylliosis.²⁰ Cortisone was prescribed for our patient but no real benefit was observed. The connective tissue invasion observed in the lungs at post-mortem appeared more extensive and somewhat less cellular than the findings noted in the biopsy specimen before the institution of cortisone therapy. It should be pointed out, however, that therapy was undertaken at a time when the destructive and invasive fibrosis was well established. It is indeed doubtful whether cortisone or, for that matter, any form of therapy would be of real value in this condition once *cor pulmonale* is manifest. Obviously, if therapy is to be of any value in diffuse interstitial pulmonary fibrosis it should be aggressively applied at an early stage, before the devastating scar tissue encroaches on the capillaries. Unfortunately, the rarity of diffuse interstitial pulmonary fibrosis, the extreme difficulty in establishing an early diagnosis and, finally, the complete ignorance as to its etiology present almost insurmountable obstacles in evaluating any form of therapy in this bizarre condition.

There has been a tendency to consider diffuse interstitial pulmonary fibrosis as a distinct disease entity. However, no etiologic agent in the various reported cases has ever been established in this condition.¹⁻¹³ Hamman and Rich¹ believed it to be related to some form of viral infection. It is interesting to note that the onset of the illness in our patient was described as a viral infection. Diffuse interstitial pulmonary fibrosis has been observed in scleroderma and diffuse (systemic) lupus erythematosus.²¹⁻²³ The inhalation of certain dusts and fumes may on occasion produce an interstitial pneumonitis leading conceivably, through failure of resolution, to interstitial fibrosis. This is suggested by Spain,¹³ who cites the experimental work of Highman²⁴ in which the inhalation of

CH_2ClBr produced interstitial pneumonia in mice. CH_2ClBr is a potential substitute for carbon tetrachloride. Beryllium poisoning, now well established as an occupational disease, may also produce an interstitial type of fibrosis of the lungs.²⁵⁻²⁶ In the present state of knowledge it would seem that diffuse interstitial pulmonary fibrosis is not a specific disease entity but is probably a syndrome produced or initiated by a variety of agents.

SUMMARY

1. A case of diffuse interstitial pulmonary fibrosis of the lungs of unknown causation is described. This is the first instance in which a correct diagnosis was established ante mortem by means of biopsy and catheterization studies.

2. The clinical course was characterized by progressive cardiac failure which obscured the primary pulmonary condition. Early in the illness a hypermetabolic state was found.

3. Cortisone therapy was instituted after the diagnosis was established. No real benefit was observed either clinically or microscopically.

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EDITORIAL

IMMUNIZATION FROM PARALYTIC POLIOMYELITIS

INFANTILE paralysis strikes its victims in such a spectacular manner and is often so devastating that it arouses consternation and general sympathy. This has stimulated a huge volume of investigation which would be out of all proportion to the importance of the disease if this were judged solely by the frequency of its occurrence. The necessity until recently of utilizing monkeys exclusively in the experimental study of the disease has greatly restricted the scope of such investigations. However, the availability of liberal grants of funds for such studies and the recent introduction of new technical procedures have rapidly advanced our knowledge of the disease. These include the adaptation to mice of certain strains of Type 2 virus, and particularly the success, first of Enders and associates¹ and later of many others, in obtaining ample growth of the virus in cultures of nonneural tissue, particularly of the testis and kidney of the monkey. There are still, however, divergent views as to many points of fundamental importance regarding the epidemiology and pathogenesis of the disease.

Infection is acquired through the gastrointestinal tract, predominantly by direct contact with cases or "carriers" (symptomless infection). Droplet infection is possible. Dissemination of the virus is also from the gastrointestinal tract, by means of the pharyngeal secretion and the feces. There is still dispute as to which practically is the more important. Although the virus is abundant in feces and although it survives for substantial periods in sewage and has been recovered from contaminated flies, there is no conclusive evidence that human infection has occurred from such sources.

It is generally agreed that for every case which shows definite paralysis, there are at least 100, perhaps 1000, cases of mild or symptomless infection. These can usually be recognized only by subsequent demonstration of specific antibodies in the blood. A few with "grip-like" symptoms may be suspected during the course of an epidemic, and an occasional one has been recognized by demonstrating the virus in the feces. The infection is therefore widely disseminated, like measles, sooner or later involving practically everyone in a community and producing a substantial degree of immunity as a result. Those who do escape infection in childhood and acquire it later are prone to suffer a more severe clinical type of the disease.

In those cases with paralysis, the virus invades the nerve cells, and there is abundant proof that the virus can reach the cells by centripetal passage through nerve trunks (axones). This may happen following a tonsillectomy or after application of virus to an exposed nerve fiber. There is also evi-

¹ Enders, J. F., Weller, T. H., and Robbins, F. C.: Cultivation of the Lansing strain of poliomyelitis virus in cultures of various human embryonic tissues, *Science* **109**: 85, 1949.

dence that in monkeys after intracerebral inoculation the virus may pass centrifugally through the axones to the exterior (pharynx).

What happens in the symptomless cases has been a matter of dispute. It has been widely held that in these cases also, virus reaches the terminal nerve fibers in the pharyngeal wall, passes centripetally to the nerve cells and multiplies exclusively in neural tissue (reviewed by Faber²). Such cases would differ from the paralytic ones only in the precise distribution or extent of the cells involved.

Recent work, however, has convinced a majority of investigators that infection occurs primarily in the wall of the gastrointestinal tract, multiplication of the virus is usually limited to this tissue, and invasion of neural tissue is a relatively rare accident, often but not necessarily disastrous when it does occur.

The question has also been raised as to whether, in those cases which become paralyzed, invasion of the nervous system may not be through the blood stream rather than through the nerve trunks.³ Attempts to demonstrate virus in the blood stream in man or monkey after the earliest manifestations of paralysis have almost uniformly failed. At this time, however, antibodies are usually demonstrable in considerable amount. Rhesus monkeys are not favorable subjects for experimental oral infection. Cynomolgus monkeys (*Macaca iris*), however, and chimpanzees behave much more like human subjects. They are readily infected by oral administration, they excrete virus in the feces for substantial periods, they may show symptoms of mild illness and they develop antibodies in the blood, but only a minority show any paralysis. It has been shown both by Bodian³ and by Horstman⁴ that virus is demonstrable in the blood of a substantial proportion of these monkeys if it is obtained a few days before the onset of paralysis. Bodian found no viremia in 11 animals which did not become paralyzed. It seems reasonably probable that a similar viremia may occur in man and that this may be the route of infection of the nervous system.

From the standpoint of immunization this is important, since relatively low titers of antibody prevent viremia and paralysis in monkeys fed virus, and this also has proved true in man. On the other hand available evidence offers little hope that antibiotics or immune antibodies will significantly alter the course of an infection after the virus has penetrated the nerve cells.

There are three antigenically distinct types of poliomyelitis virus prevalent in the United States and as far as known in the rest of the world. Infection with any one type, whether symptomless or paralytic, results in an immunity and the development of antibodies which are specific for the type and without effect on strains of the other types. To secure a complete

² Faber, H. K.: Pathogenesis and onset of symptoms of poliomyelitis, *Pediatrics* **6**: 488-497, 1950.

³ Bodian, D.: A reconsideration of the pathogenesis of poliomyelitis, *Am. J. Hyg.* **55**: 414-438, 1952.

⁴ Horstman, D. M.: Poliomyelitis virus in the blood of orally infected monkeys and chimpanzees, *Federation Proc.* **11**: 471, 1952.

immunity from infantile paralysis, one must successfully encounter all three types of virus. The majority of adults possess in their serum antibodies for one or more of these types, demonstrable by the capacity to neutralize the corresponding type of virus and presumably the result of a previous infection.

It is questionable, however, whether after a single attack a permanent effective immunity follows, comparable with that following measles or yellow fever. There is considerable evidence that continued immunity depends upon repeated exposures and subclinical reinfections, as is the case in diphtheria and hemolytic streptococcal infections.⁵ The human race and the poliomyelitis virus have become relatively well adapted to each other. The incomplete and inadequate elimination of the virus from a community, if even this were possible, or illadvised methods of immunization which would disturb this equilibrium might well do more harm than good as far as the frequency and severity of overt human illness is concerned.

A satisfactory immunizing procedure must be absolutely safe to warrant widespread use in an infection with as low a morbidity and mortality rate as in poliomyelitis. It must prevent paralysis, and it must confer an adequate and durable immunity or it must not prevent the spontaneous development of an immunity such as is acquired by most subjects under natural conditions. Merely to postpone infection would be a disservice to the individual.

Either an active or a passive immunity from poliomyelitis can be produced. Technical difficulties and inherent dangers have hitherto prevented the development of a practicable vaccine for use in man, but somewhat more progress has been achieved with passive immunization.

Passive immunization is based soundly on animal experiments. Adequate doses of immune serum protect monkeys from subsequent intracerebral injection of virus. Substantially smaller doses such as are furnished by human gamma globulin will protect from *paralysis* after intramuscular inoculation⁶ and after virus is administered orally to cynomolgus monkeys,⁷ although this does not prevent *infection*, fecal excretion of virus and the development of active immunity. Bodian has shown that human gamma globulin as prepared for the Red Cross contains antibody for all three types of virus in about equal titer. This material has been used in thousands of cases of measles and hepatitis, and its safety has been amply demonstrated, though rarely hypersensitive reactions have been observed after repeated injections. For these reasons extensive field tests were carried out by Hammon and associates in 1951 and 1952. Gamma globulin in dose of 0.1 to 0.2 ml. per pound was administered to one half of 54,772 children between the ages of one to 11 years during severe epidemics in three localities. The

⁵ Hammon, W. McD.: Immunity in poliomyelitis, *Bacteriol. Rev.* **13**: 135-159, 1949.

⁶ Bodian, D.: Experimental studies on passive immunization against poliomyelitis. I. Protection with human gamma globulin against intramuscular inoculation, and combined passive and active immunization, *Am. J. Hyg.* **54**: 132-143, 1951.

⁷ *Ibid.*: II. The prophylactic effect of human gamma globulin on paralytic poliomyelitis in cynomolgus monkeys after virus feeding, *Am. J. Hyg.* **56**: 78-89, 1952.

other half received inert material as a control. The elaborate precautions taken to ensure safety of the subjects and accuracy of the observations have been reported in detail,^{8,9} and the results obtained have just been reported.^{10,11}

In brief, during a period of observation of 14 weeks, 104 cases of paralysis occurred in the injected children, of which 31 received gamma globulin and 73 were controls. This is a significant difference. The protection was largely restricted to the second to fifth weeks, inclusive, during which time 46 cases developed in the control group and seven in the vaccinated. Before and after this period, differences, if any, were insignificant, except that in cases developing during the first week, paralysis was less severe in vaccinated subjects. No serious reactions or untoward results were observed, and there was no evidence that the injections of gelatin increased the incidence of paralysis in the control group. Furthermore this protection was accomplished by relatively low concentrations of antibody, such as can be obtained easily by active immunization with vaccine.

Although this skillfully executed investigation amply proves the potential effectiveness of the procedure, if one considers this from a severely practical standpoint, little enthusiasm can be aroused. To produce the globulin needed for a subject requires about one unit (500 ml.) blood.¹² The cost of the globulin was \$2 per ml., or from about \$10 to \$25 per subject. In order to protect one child from a paralytic attack for a period of four or at most six weeks it is necessary to inoculate from 200 to 1000 subjects, depending upon the severity (incidence of attacks) of the epidemic. In this study, in which about 27,000 children were immunized during exceptionally heavy epidemics, 42 cases of paralysis apparently were prevented—at a cost per case of paralysis prevented of about 600 pints of blood and nearly \$9,000 for the globulin alone. In an average epidemic the wastage might be twice or three times as great. If this were to be carried out on a large scale in only the most susceptible age group, it would require as much or more blood than has been currently used for all other purposes together, civilian and defense,¹² and if this were obtainable only a small fraction of it could be processed. This is obviously entirely impracticable except for limited groups in very unusual situations, and one must look to active immunization for a practical method of protection.

It has been known for many years that vaccination of monkeys with living virus can induce a high degree of resistance to subsequent intracerebral

⁸ Hammon, W. McD., et al.: Evaluation of Red Cross gamma globulin as a prophylactic agent for poliomyelitis. I. Plan of controlled field tests and results of 1951 pilot study in Utah, *J. A. M. A.* **150**: 739-749, 1952.

⁹ Ibid.: 2. Conduct and early follow-up of 1952 Texas and Iowa-Nebraska studies, *J. A. M. A.* **150**: 750-756, 1952.

¹⁰ Ibid.: Preliminary report of results based on clinical diagnoses, *J. A. M. A.* **150**: 757-760, 1952.

¹¹ Hammon, W. McD., et al.: Evaluation of Red Cross gamma globulin as a prophylactic agent for poliomyelitis, *J. A. M. A.* **151**: 1272-1285, 1953.

¹² Report and supplementary report of Committee on Blood Banks to House of Delegates, American Medical Association, Denver, Colo., Dec. 2-5, 1952, *J. A. M. A.* **150**: 1697-1698, 1952.

injections of virus of the same type. This gives rise to an active infection with some risk of paralysis in the subject. By inactivating the virus completely, usually with formaldehyde, this risk is eliminated, but the effectiveness of the vaccine is greatly diminished and far larger doses are required. Recent work of Morgan¹³ and of Howe and associates¹⁴ has proved that significant protection can be obtained in monkeys by vaccine which has entirely lost its capacity of infecting these animals. The living vaccine, however, had from 200 to 500 times the antigenic potency of the inactivated material.

The idea of using such vaccine in man is not new. Both Brodie and Kolmer some 20 years ago made fairly extensive trials of a formalinized vaccine. Protection was not clearly demonstrated, and the work was abandoned after certain subjects developed paralysis under circumstances which suggested that this was caused directly or indirectly by the vaccine. These early workers were greatly hampered by lack of adequate technical methods. In particular as a source of virus they were restricted to neural tissue of infected monkeys, which has many disadvantages. The high cost of monkeys prevented the use of sufficient animals to control their work adequately.

Human vaccination on an extensive scale seemed an utterly impracticable procedure until the revolutionary discovery of Enders and associates¹ that poliomyelitis virus can be grown in relatively unlimited amounts in cultures of nonneural tissue. In the early experiments human embryonic tissue was utilized, but later these investigators and others obtained growth of virus in cultures of foreskin and of simian as well as human testicular and renal tissue. For many purposes a roller tube containing such a tissue culture¹⁵ will serve as well as a monkey. These tubes have been used in neutralization tests to determine the type of a strain of virus and to detect and measure antibody in human serum. They may be used for the primary isolation of virus from fecal suspensions or infected neural tissue. They also furnish an abundant source of virus, free from neural tissue and relatively free from all foreign material, which can be used for the production of an efficient vaccine.¹⁶

Salk¹⁷ has recently reported a study of a formalinized vaccine containing all three types of virus, grown in tissue cultures of this kind. This was administered to 161 human subjects in two institutions, primarily to determine the safety of the vaccine and the titer of antibody obtained by the vac-

¹³ Morgan, I. M.: Immunization of monkeys with formalin inactivated virus, *Am. J. Hyg.* **48**: 394, 1948.

¹⁴ Schwerdt, C. E., et al.: Immunization of cotton rats with inactivated Lansing poliomyelitis virus. I. Inactivation by chemical agents, *Am. J. Hyg.* **53**: 121-130, 1951.

¹⁵ Youngner, J. S., Ward, E. N., and Salk, J. E.: Studies on poliomyelitis viruses in cultures of monkey testicular tissue. I. Propagation of virus in roller tubes, *Am. J. Hyg.* **55**: 291-300, 1952.

¹⁶ Howe, H. A.: Antibody response of chimpanzees and human beings to formalin-inactivated trivalent poliomyelitis vaccine, *Am. J. Hyg.* **56**: 263, 1952.

¹⁷ Salk, J. E.: Studies in human subjects on active immunization against poliomyelitis. I. A preliminary report of experiments in progress, *J. A. M. A.* **151**: 1081-1098, 1953.

ination. About half had had a recent paralytic attack of poliomyelitis. A single intradermal injection of vaccine in aqueous suspension containing all three types of virus stimulated the production of antibody for Type 2 only, under the conditions of the experiment. If the vaccine was suspended in a water-in-oil emulsion, however, the oil acted as an adjuvant and antibodies appeared in much higher titer, active on all three types of virus. In general the titers obtained were comparable to those following a spontaneous attack of the disease, and they were greater than those which Hammon et al.¹¹ found adequate in their experiments with passive immunization with human gamma globulin. Substantial concentrations were maintained during periods of observation up to four and a half months. No untoward effects from the injections were observed.

This experiment was not devised directly to demonstrate protection under natural conditions, but the results reported create a strong presumption that substantial protection was furnished, presumably of significant duration. Further work in the field on a large scale will be needed to determine these points, and such is underway. As a precautionary measure, however, it has been recommended¹² that this be carried out on a gradually increasing scale but without attempting extensive trials until 1954. Salk has well summarized the present status of his work: "Although the results . . . can be regarded as encouraging, they should not be interpreted to indicate that a practical vaccine is now at hand."

At present the only available means of protecting human subjects is by injection of human gamma globulin. The limitations and disadvantages of this have already been pointed out. Although one may hypothesize unusual situations in which this material might profitably be administered, it is obviously impracticable for widespread use. Yet the undesirable degree and the sensational and misleading nature of the publicity this material has received is sure to create a vociferous and panicky demand when the next epidemic arises, a demand which can not possibly be satisfied even though an allocating authority is established. It is important that the profession generally be prepared to meet this situation, to discourage undue diversion of human blood products from other more urgent and important needs. It is also important to stress the ineffectiveness of gamma globulin in the treatment of poliomyelitis after symptoms have appeared. To employ it for this purpose would be an unjustifiable wastage of scarce and "critical" material.

P. W. C.

¹² Rivers, T. M.: Vaccine for poliomyelitis (correspondence), *J. A. M. A.* **151**: 1224, 1953.

REVIEWS

Battle Casualties: Incidence, Mortality, and Logistic Considerations. By GILBERT W. BEEBE, Ph.D., and MICHAEL E. DE BAKEY, M.D. 277 pages; 16 x 24.5 cm. Charles C. Thomas, Springfield, Ill. 1952. Price, \$10.50.

Michael E. De Bakey and Gilbert W. Beebe commenced their collaboration on the study of battle casualties in the Office of the Surgeon General, U. S. Army, in 1943, and they have continued to be leaders in that small group of men who study this subject from the point of view of both prevention and treatment, and in order to furnish the combat services with information valuable in planning new offensive weapons.

A comprehensive introduction and five other chapters cover every phase of combat casualties as well as non-battle casualties. These include the incidence of hits and wounds, death from wounds, effectiveness of weapons, location of hits and wounds, together with logistic problems as applied to the care of the sick and wounded.

It is pointed out that during World War II no comprehensive plan existed for the careful study of all phases of battle casualties, so that the authors were forced to use material of varying excellence and accuracy. They stress that three studies by Oughterson, Hopkins and Tribby, respectively, have been of great value. These three reports are the only studies available which give accurate information on the dead. They cover only 1400 of our 175,000 killed in action in World War II.

The chapter on incidence of hits and wounds will be of great value both to military tactical and medical planners. It is of interest that of 302,000 deaths in World War II, 58 per cent were killed in action.

Death from wounding is well handled. The point is made that many who are carried on the records as killed in action died during the first hour or two due to exsanguination and could well be classified as died of wounds. The implication is made that surgeons and blood could be used closer to the front lines. The military surgeon may well be proud of the fact that compared to World War I, there was an overall saving of 45 per cent of the expected number of deaths for all arms and services. Forty-five per cent of this saving was due to improvement in the care of lower extremity wounds. There was a saving of 11 per cent for abdominal, 13 per cent head, face and neck, 14 per cent thoracic, and 11 per cent upper extremity wounds. Further figures show that head, face and neck hits have a total fatality of 47 per cent, the chest 43 per cent, and the abdomen 51 per cent. These are the type of figures which show the great need for body armor and an improved steel helmet. The analysis of the causes of death in the wounded suggests that inadequate blood and plasma were used in many cases, especially during and after surgery. There appears to have been lack of logistical planning and lack of adequate blood and plasma during many periods of World War II.

The effectiveness of weapons is analyzed. Little field data came out of World War II. The studies of Oughterson, Hopkins and Tribby are carefully presented, together with other less reliable data. This material should be of great interest to the military surgeon, the tactician and the ordnance man. The relative lethal effect of weapons is part of the interesting material in this chapter. Forty-two per cent of machine gun hits, 26 per cent of rifle hits, 15 per cent of artillery hits, 9 per cent of mortar and 5 per cent of grenade are lethal. Another interesting item deals with casualties due to United States weapons. In Oughterson's Bougainville study, 219 of 1,788 casualties were due to United States fire.

The location of hits and wounds is of incalculable importance to the military surgeon and to those interested in preventing injury and fatality by body armor and

a better helmet. These depend to a certain extent on the portion of the body exposed, protective factors and tactical situation.

A section on Body Armor discloses that despite the lack of experimental evidence, armor for ground troops was summarily dismissed by responsible military authorities early in World War II on the ground of impracticability. Indeed it was decided that no further work should be done on protective equipment for ground forces. In late 1944 and early 1945 responsible individuals began to be influenced by a few medical officers who had had combat experience. It is regretted that the authors did not give the history of this dramatic fight for armor, which commenced with the report from the medical services in the Southwest Pacific Area in 1942. The Ordnance Department designed the Army Vest T-62 which weight for weight was 40 per cent more effective than our present steel helmet. Body Armor was adopted by the Ground Forces in May, 1945. The war ended before it was used in combat. The book freely quotes from the May 31, 1945 issue of the secret publication of the Surgeon General's Office "Health." It is estimated that the vest which covered 65 per cent of the trunk would have easily prevented 12 per cent of our expected dead and 8 per cent of our expected wounded. The Air Force flack suit used in World War II prevented approximately 20 per cent of fatal hits. In no uncertain terms it is suggested that an honest effort be made to use and evaluate body armor. It is tragic in view of this information that many men lost their lives in World War II because of lack of foresight. An even more tragic situation exists in that our military department failed to make use of body armor until recently. Thousands of lives have been lost due to complacency about proved equipment which should have been ready for the battle in Korea. If anyone doubts the value of body armor and the need for an improved helmet, let him consult the illustrations from Oughterson's report of 1945, pages 184-185, which show mortal wounds of entrance in 104 autopsies.

The chapter on logistics gives evidence that surgical specialists are as necessary in the forward areas as they are in base hospitals. It points the way to reduction in mortality and morbidity. The section by Dr. Edward D. Churchill stresses the need for selective evacuation of casualties based on their needs and the need for wound surgery.

It is hoped that much of the information in this book has been available to those responsible for the conduct of the Korean War. It is especially hoped that the Surgeon General's Office has made adequate allowance for research projects to study all phases of battle casualties.

We are of the opinion that this book should be in the hands of everyone, medical and non-medical, who has any interest in the care and prevention of casualties. De Bakey and Beebe have performed a fine service and no doubt their work is already responsible for the saving of many lives. The book might well serve as a textbook to be used in a course on battle casualties which should be compulsory for all Army officers.

I. RIDGEWAY TRIMBLE, M.D.

JAMES E. T. HOPKINS, M.D.

Shock and Circulatory Homeostasis. Edited by HAROLD D. GREEN, M.D., Professor of Physiology and Pharmacology, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, North Carolina. Corlies, Macy & Co., Inc., New York. 245 pages; 15.5 x 23.5 cm. 1952. Price, \$3.50.

This extremely interesting volume is the record of the transactions of the First Conference on Shock and Circulatory Homeostasis sponsored by the Josiah Macy, Jr., Foundation. In it are related the provocative and stimulating ideas of the leading workers in the field as they met and discussed their work. This form of presentation reveals the advancing front of scientific endeavor and lays bare the gaps in our knowledge. The subjects considered are humoral, vasoactive, and other metabolic derange-

ments in shock, the nervous system in shock, acute and chronic hypotension after hemorrhage in man, the infectious element in shock, and the therapeutic implications of current concepts of shock. Each chapter is full of vital information, informally presented and critically appraised. The reader is kept abreast of current thinking in the field.

This book is strongly recommended to all clinicians and investigators who are interested in problems of the circulation.

S. S.

Bodily Physiology in Mental and Emotional Disorders. By MARK ALTSCHULE, M.D., Assistant Professor of Medicine, Harvard Medical School, Boston. 228 pages, 14.5 x 22.5 cm. Grune & Stratton, Inc., New York. 1953. Price, \$5.75.

This author sets out to bring order into a field beset by "systems of thought that require no evidence" (p. 93). "Psychodynamic interpretations . . . have nothing to support them except the belief of their proponents" (p. 68). Therefore, in spite of fear that "physicians trained in psychiatry in America will understand little of the contents of this book" (p. 3), the author undertakes a pedestrian review of the literature "actually containing data" (p. 1). "The difficulty created by the lack of a satisfactory definition (not characterization) of neurosis will have to be ignored in the present work" (p. 2), and so mental diseases are classified as either neurosis or psychosis. Seventeen chapters are included with headings ranging from "Circulation" (Chapter 1) to "Sensory Functions. Neuromuscular Functions. Autonomic Reflexes" (Chapter 17). In spite of ample redundancy, certain errors mar this presentation of facts. The classic work of Hickam et al. is presented in such a way as to make it seem that these workers deny the occasional occurrence of decreased cardiac output during emotional stress (pages 6-7). The pharmacology of epinephrine and nor-epinephrine is confused by statements such as: ". . . epinephrine constricts capillaries and veins and diminishes blood flow . . ." (p. 12). The work of Sabbath and Luce is ignored and the author states confidently, "When psychosis develops in patients with asthma, the latter disappears." This half truth is then explained by the "adrenocortical hyperactivity that occurs commonly in manic depressive, schizophrenic and involutional psychoses" (p. 70). Although Mahl's work is referred to following the statement that "Emotion causes greatly varying changes in the volume and acidity of gastric secretion" (p. 84), we find on the following page a disclaimer for any concept that might explain why one autonomic division might predominate over another at a given time. The pertinent work of Lacey and co-workers is honored along with contributions of Selye and others by being conspicuously omitted.

One could document many other questionable statements, half truths and mistakes including the sentence on page 202 which states that flicker fusion frequency is a measure of the efficiency of ocular muscles! Such a documentation of errors would, however, tend to obscure the real value of this book. In actual fact, many statements in this volume are quite reasonable, and the book should be of great service to workers who by dint of familiarity with current literature and classic works can utilize the bibliographies without being confused by the accompanying text.

E. C.

Unipolar Lead Electrocardiography and Vectorcardiography. 3rd Ed. By EMANUEL GOLDBERGER, M.D., F.A.C.P., Associate Attending Physician, Montefiore Hospital, New York. 601 pages; 15.5 x 24 cm. Lea and Febiger, Philadelphia. 1953. Price, \$10.00.

This is the third edition of the author's text on electrocardiography. This edition differs from the earlier ones in many ways, especially in the addition of a large

section on vectorcardiography. As he states in the Preface, "For the past nine years I have been interested in the theoretical aspects of vectorcardiography and in this time developed several methods by which vectorcardiograms can be derived and analyzed from the electrocardiogram, and which I had previously never published."

Unfortunately, the author carries the schism implied in the title to the text as well. The section on vectors does not influence the section on electrocardiography and is not utilized to clarify electrocardiographic concepts. Many of the statements are arbitrary and contrary to documented and previously published work by others which is readily available. The absence of recorded vectorcardiograms is confusing, since the critical reader would desire to see the records upon which are based the author's numerous conclusions, including his preference for derived vectorcardiograms over recorded vectorcardiograms. The total lack of a unified concept is striking and disappointing. Of incidental annoyance to the scientific reader is the constant use of the vertical pronoun. The reviewer can not recommend this text to either student or clinician.

L. S.

Physiologic Therapy for Obstructive Vascular Disease. Modern Medical Monographs 6. By ISAAC STARR, M.D., Hartzell Research Professor of Therapeutics, School of Medicine, University of Pennsylvania, Philadelphia, Pa. 38 pages; 14.5 × 22.5 cm. Grune & Stratton, New York. 1953. Price, \$2.50.

This is a brief monograph, well worth reading, on trends in therapy in the treatment of peripheral vascular disease.

The influence of George E. Brown in the field of peripheral vascular disease is briefly summarized, as well as attitudes in therapy previous to 1928. The transition toward conservative treatment based on physiologic principles is stressed.

The histamine test and its concept is described.

Physiological methods of treatment comprise: (1) Reducing as much as possible the need for blood in the area supplied by the obstructed vessels; (2) increasing the supply of blood as much as possible by dilating the vessels still remaining open. Postural exercises; Saunders rocking bed; and suction and pressure devices are evaluated.

The importance of the best position for the diseased limb, the value of sympathectomy, as well as newer methods of treatment and prevention are stressed.

G. H. Y.

Symposium on Radiobiology. Edited by JAMES J. NICKSON, M.D., Member of the Sloan Kettering Institute, Director of the Department of Radiation Therapy of Memorial Hospital, New York, Associate Professor of Radiology, Cornell University School of Medicine. 465 pages; 15 × 23.5 cm. John Wiley & Sons, Inc., New York. 1952. Price, \$7.50.

Symposium on Radiobiology consists of 23 essays and discussions presented at the Oberlin Symposium on Radiobiology in June, 1950. These essays deal with four inter-related phases of radiobiology: (1) the physical interaction of ionizing radiation and matter; (2) the chemical changes arising from the transfer of physical energy; (3) the biochemical effects of irradiation and (4) the changes occurring in living tissues.

These scientists have brought together much heretofore isolated information and developed it into organized concepts. Both fundamental and complex concepts are presented.

While these essayists have performed an excellent task in summarizing our present knowledge of radiobiology, this book is difficult to read and understand. It

will have appeal only to those few therapeutic radiologists, biochemists and physiologists interested in this subject.

J. M. D.

Nutrition and Diet in Health and Disease. 6th Ed. By JAMES S. McLESTER, M.D., and WILLIAM J. DARBY, M.D., Ph.D. 710 pages; 16 × 24.5 cm. W. B. Saunders Co., Philadelphia. 1952. Price, \$10.00.

This is a well established textbook. Starting with a brief survey of the physiology of digestion and internal metabolism, it proceeds with a scholarly presentation of the knowledge of the various foodstuffs. Diseases or groups of diseases in which dietary considerations are important are then discussed. These discussions are introduced by comments on various basic aspects of the conditions. The dietary considerations appropriate to these conditions are then thoroughly presented. The material is well up-to-date and is well selected and evaluated. Where controversies exist, both sides are presented.

The text is abundantly documented by references to the original literature. Diet lists and other extensive tables of data are given which fulfill the practical needs of the physician in managing the dietary problems of medical practice.

G. E. G.

BOOKS RECEIVED

Books received during April are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

An Atlas of Surgical Exposures of the Extremities. By SAM W. BANKS, M.D., Associate Professor of Orthopaedic Surgery, Northwestern University Medical School, etc.; and HAROLD LAUFMAN, M.D., Ph.D., Associate Professor of Surgery and Director of Experimental Surgery, Northwestern University Medical School, etc. 391 pages (552 illustrations on 179 plates); 28 × 20 cm. 1953. W. B. Saunders Company, Philadelphia. Price, \$15.00.

Bodily Changes in Pain, Hunger, Fear and Rage. 2nd Ed. By WALTER B. CANNON, M.D., S.D., LL.D., George Higginson Professor of Physiology in Harvard University. 404 pages; 21 × 14 cm. 1953. Charles T. Branford Company, Boston. Price, \$5.00.

Clinical Diagnosis by Laboratory Methods: A Working Manual of Clinical Pathology. 12th Ed. By JAMES CAMPBELL TODD, Ph.B., M.D., Late Professor of Clinical Pathology, University of Colorado School of Medicine; ARTHUR HAWLEY SANFORD, A.M., M.D., Emeritus Professor of Clinical Pathology, The Mayo Foundation, University of Minnesota, etc.; and BENJAMIN B. WELLS, M.D., Ph.D., Professor of Medicine, Department of Medicine, School of Medicine, University of Arkansas. 998 pages; 24 × 16 cm. 1953. W. B. Saunders Company, Philadelphia. Price, \$8.50.

The Conception of Disease: Its History, Its Versions and Its Nature. By WALTHER RIESE, M.D. 120 pages; 22.5 × 14 cm. 1953. Philosophical Library, New York. Price, \$3.75.

Diagnostic Tests in Neurology: A Selection for Office Use. By ROBERT WARTENBERG, M.D. Forewords by SIR GORDON HOLMES, M.D., F.R.S., and by STANLEY TRUMAN, M.D. 228 pages; 21 × 14.5 cm. 1953. The Year Book Publishers, Inc., Chicago. Price, \$4.50.

Epidemiology and Control of Endemic Syphilis: Report on a Mass-Treatment Campaign in Bosnia. World Health Organization Monograph Series No. 11. By E. I. GRIN, M.D., Director, Central Dispensary for Skin and Venereal Diseases, Sarajevo, Yugoslavia. 93 pages; 24 × 16 cm. (paper-bound). 1953. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, \$1.00.

Expert Committee on Hepatitis: First Report. World Health Organization Technical Report Series No. 62. 26 pages; 24 × 16 cm. (paper-bound). 1953. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 20 cents.

From the Workshop of Discoveries. Porter Lectures, Series 19. By OTTO LOEWI, Research Professor of Pharmacology, New York University College of Medicine. 62 pages; 21.5 × 14 cm. 1953. University of Kansas Press, Lawrence, Kansas. Price, \$2.00.

Guide for National Studies of Nursing Resources. Bulletin of the World Health Organization, Supplement 7. By MARGARET G. ARNSTEIN, R.N., M.P.H., Chief, Division of Nursing Resources, United States Public Health Service, etc. 36 pages; 24 × 16 cm. (paper-bound). 1953. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 20 cents.

Hypersplenism and Surgery of the Spleen. By WILLIAM DAMESHEK, M.D., and C. STUART WELCH, M.D., Pratt Diagnostic Hospital, New England Center Hospital and Tufts College Medical School, Boston, Massachusetts. Based on Exhibits presented at the Annual Meetings in 1947 and 1951 of the American Medical Association; Recipients in 1951 of the A. M. A. Silver Medal. 84 pages (one side only); 30.5 × 23 cm. (loose-leaf). 1953. Grune & Stratton, Inc., New York. Price, \$10.00.

Overeating, Overweight and Obesity: Proceedings of the Nutrition Symposium Held at the Harvard School of Public Health, Boston, Massachusetts, October 29, 1952. Nutrition Symposium Series Number 6. By DAVID P. BARR, JOHN R. BROBECK, HENRY W. BROSIEN, LOUIS I. DUBLIN, FRANK A. EVANS, P. C. FRY, SAMUEL GURIN, PAUL GYÖRGY, EDWARD E. HUNT, JR., ANCEL KEYS, P. S. PECKOS and A. W. PENNINGTON. 151 pages; 23 × 15.5 cm. (paper-bound). 1953. The National Vitamin Foundation, Incorporated, New York. Price, \$1.50.

Physical Examination of the Surgical Patient. By J. ENGLEBERT DUNPHY, M.D., F.A.C.S., Associate Clinical Professor of Surgery, Harvard Medical School, etc.; and THOMAS W. BOTSFORD, M.D., F.A.C.S., Clinical Associate in Surgery, Harvard Medical School, etc. 326 pages; 24 × 16 cm. 1953. W. B. Saunders Company, Philadelphia. Price, \$7.50.

Physiological Foundations of Neurology and Psychiatry. By ERNST GELLHORN, M.D., Ph.D., Professor of Neurophysiology, University of Minnesota. 556 pages; 24 × 15.5 cm. 1953. The University of Minnesota Press, Minneapolis, Minnesota. Price, \$8.50.

Probleme der Morphologie Cytochemie und Wuchsform des Tuberkuloseerregers. By DR. MED. FRIEDRICH J. BASSERMANN. 98 pages; 24 × 17 cm. (paper-bound). 1953. Georg Thieme Verlag, Stuttgart; agents for U. S. A.: Grune & Stratton, Inc., New York. Price, kart. DM 7.80.

- Sandoz Atlas of Haematology.* Written and compiled by DR. E. UNDRITZ, of the Sandoz Pharmacological Research Laboratories, under the direction of PROF. E. ROTHLIN; translated into English by DR. A. M. WOOLMAN. 102 pages, with 44 color plates; 29.5 × 25.5 (loose-leaf). 1952. Sandoz, Ltd., Basel, Switzerland. Price, \$7.00.
- Visceral Circulation. A Ciba Foundation Symposium.* Chairman: PROFESSOR J. McMICHAEL, M.D., F.R.C.P., F.R.S. Ed. Editor for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch.; assisted by MARGARET P. CAMERON, M.A., A.B.L.S., and JESSIE S. FREEMAN, M.B., B.S., D.P.H. 278 pages; 21 × 14 cm. 1953. Medical Book Department, Little, Brown & Company, Boston. Price, \$6.50.
- Working Conference on Nursing Education: Report. World Health Organization Technical Report Series No. 60.* 30 pages; 24 × 16 cm. (paper-bound). 1953. World Health Organization, Geneva; available in U. S. A. through Columbia University Press, International Documents Service, New York. Price, 20 cents.
- X-Ray Sieve Therapy in Cancer: A Connective Tissue Problem.* By BENJAMIN JOLLES, M.D., D.M.R., Consultant Radiotherapist, Physician i/c Radiotherapy Department, General Hospital, Northampton, etc.; with a Foreword by SIDNEY RUSS, C.B.E., D.Sc., F. Inst. P., Professor Emeritus, Middlesex Hospital, etc. 192 pages; 22 × 14 cm. 1953. Little, Brown and Company, Boston. Price, \$6.00.



LEROY H. SLOAN

LEROY H. SLOAN, M.D., F.A.C.P., PRESIDENT, AMERICAN COLLEGE OF PHYSICIANS

LEROY H. SLOAN—B.S., M.D., F.A.C.P., 5800 Stony Island Avenue, Chicago 37, Ill. Born, October 7, 1892, Aurora, Ill. B.S., 1914, University of Chicago; M.D., 1917, Rush Medical College. Member, Phi Beta Kappa, Sigma Xi and Alumni Member, Alpha Omega Alpha Fraternities. Assistant in Physiology, University of Chicago, 1914-15; Fellow in Pharmacology, Northwestern University Medical School, 1915-16; Postgraduate Study, University of Pennsylvania, Harvard Medical School, University of Vienna and National Hospital, Queens Square, London; formerly Associate Clinical Professor of Medicine, Rush Medical College; Associate Professor of Medicine, 1935-39, and Professor of Medicine since 1939, University of Illinois College of Medicine; Director of Medical Service, Illinois Central Hospital; Consulting Physician, Copley Memorial Hospital (Aurora); formerly Attending Physician, Cook County Hospital and Associate Attending Neurologist, St. Luke's Hospital; served during World War I in the Medical Corps, U. S. Army, and during World War II as Chairman of Region XIV, War-Time Graduate Medical Meetings; Diplomate, American Board of Internal Medicine and National Board of Medical Examiners; former President, Chicago Society of Internal Medicine; former Member, Board of Governors, Institute of Medicine of Chicago; former Secretary and Chairman of the Section on Medicine, Illinois State Medical Society, Jackson Park Branch; Fellow, American Medical Association; Member, Central Clinical Interurban Society; Chairman, Committee of the Body as a Whole, Standard Nomenclature, A.M.A.; author of numerous published medical articles; Collaborating Editor, Merck's Manual and Year Book of General Therapeutics (Year Book Publishers); Editor, Section on Appendicitis, Tice System of Medicine; Editor, Therapy of Cook County Hospital, 1940-41.

Dr. Sloan became a Fellow of the American College of Physicians in 1929, was for a number of years its Governor for Northern Illinois, was the General Chairman of the 28th Annual Session, Chicago, Ill., April 28-May 2, 1947, and has served as Regent since 1944. He has served on many important committees of the College, and at present is the official representative of the College on the Advisory Committee and on the Board of Commissioners of the Joint Commission on Accreditation of Hospitals. He was made President-Elect at the Cleveland Annual Session of the College on April 24, 1952, and was inducted as President at the Atlantic City Annual Session on April 16, 1953.



CYRUS CRESSEY STURGIS

CYRUS CRESSEY STURGIS, B.S., M.D., F.A.C.P., PRESIDENT-ELECT,
AMERICAN COLLEGE OF PHYSICIANS

CYRUS CRESSEY STURGIS—Thomas Henry Simpson Memorial Institute for Medical Research, Ann Arbor, Mich. Born, April 2, 1891, Pendleton, Ore. B.S., 1913, University of Washington; M.D., 1917, Johns Hopkins University School of Medicine. Medical House Officer (1917-18), Assistant Resident Physician (1919-20), Resident Physician (1920-22), Peter Bent Brigham Hospital, Boston, Mass.; First Lieutenant, (MC), U. S. Army (1918-19); Teaching Fellow (1920-22), Faculty Instructor (1922-25), Assistant Professor of Medicine (1925-27), Harvard Medical School; Physician (1925-27), Peter Bent Brigham Hospital; Associate Physician (1925-26), Collis P. Huntington Hospital, Boston, Mass.; since July, 1927, Director of the Thomas Henry Simpson Memorial Institute for Medical Research and Professor of Internal Medicine, University of Michigan Medical School; since 1928, Director, Department of Internal Medicine, University of Michigan Hospital; Author, "Hematology" (Charles C. Thomas, 1948); Contributor to Cecil's Textbook of Medicine, Musser's Textbook of Medicine and author of numerous articles in the field of Hematology and Internal Medicine; Diplomate, American Board of Internal Medicine; former President, Central Society for Clinical Research and Interstate Postgraduate Medical Association; Member, Michigan State Medical Association, American Medical Association, American Society for Clinical Investigation, American Clinical and Climatological Association, American Association for Advancement of Science, American Goiter Association and Association of American Physicians; Chevalier, Legion of Honor (France); Fellow of the American College of Physicians since 1928, Regent since 1947; served on many important committees of the College, including particularly the Committee on Fellowships and Awards, which administers the Research Fellowship Program and the W. K. Kellogg Foundation-American College of Physicians Latin-American Fellowship Programs.

Dr. Sturgis was elected unanimously as President-Elect of the College at the Atlantic City Annual Session, April 16, 1953, and will serve as President, 1954-55.

COLLEGE NEWS NOTES

THE ATLANTIC CITY ANNUAL SESSION

The Thirty-Fourth Annual Session of the American College of Physicians was held at Atlantic City, April 13-17, 1953, under the Presidency of T. Grier Miller, M.D., Philadelphia, Pa., and the General Chairmanship of Hilton S. Read, M.D., Atlantic City, N. J. Planning of an Annual Session of the College in a city where there are few hospitals and no medical schools was approached with some temerity because hospital clinics in the past have constituted a major item on the program. Obviously a different type of program had to be arranged and substitutions made. The General Chairman and his Committeemen materially expanded the program of Panel Discussions, Clinical-Pathological Conferences and Televised Color Clinics. They further initiated a series of "Meet the Expert" lectures or panel-like programs. They also introduced many new features of entertainment, features that in some instances had never appeared on a College program, such as trap shooting and golf tournaments, a variety program of divertissement and a concert by the famed Philadelphia Orchestra.

According to the evaluation made by physicians in attendance thus far, this new program was exceedingly well received and few indeed were those who expressed disappointment in not having the usual program of hospital clinics. A more extensive evaluation of the meeting is being made through the Board of Governors and their constituents and the findings will be used for the advice and direction of those responsible for the Annual Session program in Chicago, April 5-9, 1954.

Among highlights of the meeting were the James D. Bruce Memorial Lecture on Preventive Medicine, "Influenza; The New Acquaintance," by Dr. Thomas Francis, Jr., Henry Sewell Professor of Epidemiology and Chairman of the Department, University of Michigan, and the John Phillips Memorial Lecture, "The Action of Insulin," by Dr. Charles H. Best, Professor of Physiology and Director of the Banting and Best Department of Research Medicine, University of Toronto School of Medicine, Ont. At the Convocation these individuals were awarded the James D. Bruce Memorial Medal in Preventive Medicine and the John Phillips Memorial Medal in Internal Medicine, respectively. Also at the Convocation Dr. A. Blaine Brower, Dayton, Ohio, was awarded the Alfred Stengel Memorial Diploma, his citation reading, "Dr. A. Blaine Brower, a recipient of the degrees of Bachelor of Arts and Doctor of Medicine from the University of Michigan. He was elected a Fellow of this College in 1926, and served as its Governor for Ohio from 1931 to 1946. He was Second Vice President, 1946-1947. In 1947 he was elected to the Board of Regents and worked tirelessly as a Regent for six years. In these various offices he served with distinction. His Governorship was a model for future Governors of the College. For 15 years he traveled widely through the State of Ohio to become personally acquainted with all the candidates and their qualifications for membership. As a member of the Committee on Credentials he scrutinized proposals for membership with great diligence, and as Chairman of the Committee on Finance and the Committee on Insurance he displayed remarkable acumen. He has supported and promoted the highest possible standards of membership and traditions of the College. A firm advocate of postgraduate education, in 1950 he created a substantial endowment trust for traveling scholarships, in order to provide an opportunity for worthy young physicians, preferably Associates of the College, to spend a few weeks as visiting scholars at institutions for observation and study. The Board of Regents became so impressed with the practical work of these Fellowships that it doubled the endowment trust to provide an additional Fellowship, starting in 1952. As an internist he has attained eminence. Through his example and encouragement many young physicians

have been launched on a career of service to man." Another highlight of the Convocation was the conferring of Masterships on Dr. Reginald Fitz of Boston, and on Dr. Francis M. Pottenger, Sr., of Monrovia, Calif.

Dr. Cyrus C. Sturgis, Professor of Medicine and Director of the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan Medical School, Ann Arbor, was made President-Elect, and Dr. LeRoy H. Sloan of Chicago was inducted as President. Other elections include: Dr. George F. Strong, Vancouver, B. C., First Vice President; Dr. Alex. M. Burgess, Sr., Providence, R. I., Second Vice President; Dr. William C. Chaney, Memphis, Tenn., Third Vice President. Elected to the Board of Regents for the term of three years were Dr. Eugene B. Ferris, Atlanta, Ga., Dr. Philip S. Hench, Rochester, Minn., Dr. Chester S. Keefer, Boston, Mass., Dr. George H. Lathrope, Morristown, N. J. (re-elected), Dr. T. Grier Miller, Philadelphia, Pa. Dr. Richard A. Kern and Dr. William D. Stroud, both of Philadelphia, were re-elected as Secretary General and Treasurer, respectively. Personnel of the Board of Governors appears elsewhere in this issue, but the following were new elections to that Board: Dr. Richard P. Stetson, Boston, Governor for Massachusetts; Dr. H. Archibald Des Brisay, Vancouver, Governor for British Columbia; Dr. Amadeo Vicente-Mastellari, Panama, Governor for Panama and the Canal Zone; Dr. Willis M. Fowler, Iowa City, Governor for Iowa, Dr. H. Marvin Pollard, Ann Arbor, Governor for Michigan, Dr. Carl V. Moore, St. Louis, Governor for Missouri, Dr. Sven M. Gundersen, Hanover, Governor for New Hampshire, Dr. Marshall N. Fulton, Providence, Governor for Rhode Island, Dr. Clyde W. Holland, Halifax, N. C., Governor for the Maritime Provinces.

Standing Committees were appointed by the Regents and/or the President for 1953-54, personnel of which will be published elsewhere in this journal. It was announced that the Thirty-Fifth Annual Session of the College will be held in Chicago, April 5-9, 1954, and the Thirty-Sixth Annual Session will be held in Philadelphia, Pa., April 25-29, 1955. Dr. Howard Wakefield of Chicago was appointed General Chairman of the Thirty-Fifth Annual Session and Dr. Thomas M. Durant, Philadelphia, Pa., was appointed General Chairman of the 1955 Annual Session.

The Atlantic City Session of the College was the second largest on record, being exceeded only by the New York Session in 1949. A summary of the attendance for the past five years follows:

	Members	Guest Physicians	Guest Non-Physicians	Students	Exhibitors	Ladies	Total
Atlantic City (1953)	2,316	1,057	43	15	484	1,063	4,978
Cleveland (1952)	2,000	1,191	26	84	451	684	4,436
St. Louis (1951)	1,564	720	23	13	464	475	3,259
Boston (1950)	2,091	1,225	42		591	840	4,789
New York (1949)	2,486	1,471	38		665	967	5,627

ACP GROUP INSURANCE PLANS

On April 15, 1953, during the Atlantic City Annual Session of the College it was announced by President T. Grier Miller that the requisite percentage of the members had applied for the Health and Accident Plan and that accordingly the Plan became effective as of that day. This means that all of the members of the American College of Physicians who had sent in their applications and were actively at work on a full-time basis that day were immediately covered. Those not at work at that time because of incapacitation will be covered 30 days after their return to full-time work.

It was indeed gratifying that the College Plan qualified in so short a time after the original announcement of its availability, especially since that was accomplished by mail, without the instrumentality of solicitation by sales representatives. As this report is being prepared, it seems very possible that by the closing date of the plan, June 1, 60 to 65 per cent of the eligible members will have subscribed.

An effort is being made to get the carrier, Educators Mutual Insurance Company, to hold the subscription list open a brief additional time to accommodate those who have thus far procrastinated. When the Plan is finally closed, those who apply will be subject to physical scrutiny. However, newly elected members (Associates and Direct Fellows elected at the Atlantic City Annual Session, April 12, 1953) will be eligible for the Plan if they submit applications within 60 days after formal notifications of election were mailed.

Malpractice insurance generally is in a state of flux. Many carriers have found it necessary to increase their rates when current policies expire. Malpractice suits have materially increased in number and costs have been steadily rising. The Malpractice Plan adopted by the College is also in force and providing protection for many of our members, but it has not been as widely used as had been expected. It has been ascertained that in some limited areas, not nation-wide, individual policies at lower rates than under the ACP Plan are occasionally available. This is a situation that will be rectified, if possible. Members who have been quoted lower rates than those provided by the ACP Plan are urged to send the name of the company and a copy of the quotation to the ACP Association Service Office, 1500 Walnut St., Philadelphia 2, Pa., which may be helpful to the College in obtaining lower rates from its present carrier. Remember, the ACP Plan is yours and can only be as favorable for all members as they help to make it. The underwriters have agreed to review this situation during August, if the members have by that time submitted enough factual information on which to base a decision. Our Association Service Office must have actual, definite information—name of company, rates, if possible a copy of the policy, whether an individual or group plan.

AUDITOR'S REPORT, 1952 OPERATIONS

David Robinovitz
Accountant and Auditor
Philadelphia, Pa.

February 15, 1953

To the Board of Regents
American College of Physicians, Inc.
4200 Pine Street
Philadelphia 4, Pa.

Mr. E. R. Loveland, Executive Secretary

Dear Sir:

I have examined the accounts of the

AMERICAN COLLEGE OF PHYSICIANS, INC.

for the year ending December 31, 1952, and the accompanying statements, including the Balance Sheet at December 31, 1952, the analyses of the General Fund and the Endowment Fund and the Statement of Income Account for the calendar year 1952 are in accordance with the books of Account, and in my opinion present fairly the financial position at December 31, 1952 and the results of operations for the calendar year 1952, in conformity with generally accepted accounting principles applied on a basis consistent with that of preceding years, and subject to the following comments:

Cash: The cash was properly accounted for, was confirmed by direct correspondence with the following depositories, and the Petty Cash verified:

Girard Trust Corn Exchange Bank, Philadelphia.....	\$ 77,610.04
Provident Trust Company, Philadelphia.....	29,052.77
Royal Bank of Canada, Montreal.....	2,798.65
Petty Cash.....	250.00
	<u>\$ 109,711.46</u>

Accounts Receivable: The Accounts Receivable were examined and found to be less than one year old and appear to be collectible. The detailed accounts receivable were in agreement with the control account. No requests for confirmation of the accounts were mailed.

Investments: The securities were accounted for by direct correspondence and the income for the period under review was verified. The investment transactions are recorded properly in the general books of accounts and in the Investment Ledger, which is in agreement with the investment accounts of the General Ledger.

General: The changes in the amount of the Endowment Fund and the General Fund during the year 1952 are as follows:

	Balance Jan. 1, 1952	Balance Dec. 31, 1952	Increase
Endowment Fund.....	\$ 347,079.60	\$ 382,598.64	\$ 35,519.04
James D. Bruce Fund.....	10,000.00	10,000.00	
A. Blaine Brower Fund.....	20,000.00	20,000.00	
General Fund.....	508,144.00	576,555.52	68,411.52
	<u>\$ 885,223.60</u>	<u>\$ 989,154.16</u>	<u>\$ 103,930.56</u>

The Executive Secretary has analyzed the income of the ANNALS OF INTERNAL MEDICINE according to Volume, so that the income and expenses are stated according to the year of publication, with the exception of Volumes of prior years, which are closed out and not carried in an inventory account, with the sales properly credited to the General Fund according to the date of sale.

General Comments: The prepaid insurance at December 31, 1952, was not set up as a deferred expense; the other deferred and accrued items were verified; the charges to the Furniture and Equipment Accounts represent proper additions to the account, and the allowances for depreciation appear to be adequate. A depreciation reserve account has been set up for the Headquarters Building in accordance with the action of the Board of Regents at the meeting on December 12, 1937, which provided that depreciation on the Building should be taken into account at the rate of \$1,000.00 per year and increased in 1949 to \$2,000.00. The footings and extensions of the inventory were verified.

All ascertainable liabilities have been included in the Balance Sheet.

All recorded receipts from dues, initiation fees, exhibits, advertising, sales of publications, etc., were properly deposited in banks and all disbursements, as indicated by the vouchers, cancelled checks and bank statements were properly recorded in the books of account.

Respectfully submitted,

(Signed) DAVID ROBINOVITZ, Auditor

*Summary of Operations for the Calendar Year 1952**Income:*

Annual Dues.....	\$ 52,741.41
Initiation Fees.....	17,950.00
Subscriptions, ANNALS OF INTERNAL MEDICINE.....	131,920.26
Advertising, ANNALS OF INTERNAL MEDICINE.....	56,780.85
Income from Investments, General Fund (including Accrued)...	20,582.41
Income from Investments, Endowment Fund (including Accrued)	15,632.11
Dividend on Perpetual Insurance Deposit.....	90.00
Sale of 1951 Directory.....	317.70
Postgraduate Courses, Balance.....	2,336.13
Rent—404-12 S. 42nd Street (net).....	1,205.49
Profit on Sale or Maturity of Securities, General Fund.....	8,684.68
Profit on Sale of Equipment Traded In.....	18.20
Thirty-third Annual Session:	
Exhibits.....	\$ 34,540.25
Guest Fees.....	7,345.00
Banquet.....	48.80
	41,934.05

TOTAL INCOME..... \$ 350,193.29

Expenses:

Salaries.....	\$ 68,266.54
Communications.....	10,975.98
Office Supplies and Stationery.....	3,268.60
Printing.....	93,144.86
Traveling Expenses.....	13,722.54
Maintenance.....	119.93
Miscellaneous.....	1,736.49
College Headquarters—Maintenance, Taxes, Insurance, etc.....	9,967.56
Depreciation on College Headquarters Building.....	2,000.00
Depreciation on Furniture and Equipment.....	1,697.76
Keys, Pledges and Frames.....	255.83
Regional Meetings.....	5,652.60
John Phillips Memorial Prize.....	353.40
Investment Counsel Service and Security Custodian's Fee.....	1,041.00
Employees' Pension Fund.....	6,843.99
Bad Debts.....	75.50
Advertising Discount.....	1,249.91
1952 Directory Supplement.....	1,519.59
Loss on Sale of Securities, General Fund.....	533.93
Joint Commission on Accreditation of Hospitals.....	14,288.37
Collection and Exchange.....	29.67
Conference Committee on Graduate Training in Medicine.....	186.97
Group Insurance Survey.....	244.91
Thirty-third Annual Session—Special Expenses:	
Committee on Panels.....	408.19
Committee on Publicity.....	697.63
Committee on Ladies' Entertainment.....	1,892.70
Ladies' Subscription Dinner.....	25.71
Committee on Clinics.....	203.75
Convocation.....	1,479.66
Governors-Regents Dinner.....	898.58
Registration.....	887.63
Television Program.....	32.50
Orpheus Male Chorus.....	705.75
Scientific Exhibit.....	735.00
Rent.....	9,229.16
Other Miscellaneous.....	2,943.58

TOTAL EXPENSES..... \$ 257,315.77

Net Income for 1952 Credited to General Fund..... \$ 92,877.52

ACP POSTGRADUATE COURSES

The Committee on Postgraduate Courses and the Regents of the College have approved the following postgraduate courses. The detailed Bulletin with all data included will be published in early July. Matriculation fees: ACP Members, \$30.00; Non-members, \$60.00. Registration forms will accompany the Bulletin.

Autumn, 1953

- CARDIOVASCULAR DISEASES: New York University College of Medicine, New York, N. Y.; Charles E. Kossman, M.D., F.A.C.P., Director; One week, October 12-17.
- CLINICAL NEUROLOGY: Jefferson Medical College of Philadelphia, Philadelphia, Pa.; Bernard A. Alpers, M.D., F.A.C.P., Director; One week, date to be determined.
- INTERNAL MEDICINE: University of Chicago School of Medicine, Chicago, Ill.; Wright R. Adams, M.D., F.A.C.P., Director; One week, October 19-23.
- SEMINARS IN INTERNAL MEDICINE: Vanderbilt University School of Medicine, Nashville, Tenn.; Rudolph Kampmeier, M.D., F.A.C.P., and Hugh J. Morgan, M.D., F.A.C.P., Co-directors; One week, October 19-25.
- PHYSIOLOGICAL BASIS OF INTERNAL MEDICINE: Duke University School of Medicine, Durham, N. C.; Eugene A. Stead, Jr., M.D., F.A.C.P., Director; One week, date to be determined.
- PRESENT DAY THERAPY AND ITS PHYSIOLOGIC BASIS: University of Utah College of Medicine, Salt Lake City, Utah; Maxwell M. Wintrobe, M.D., F.A.C.P., Director; One week, either November 16-20 or 9-13.
- THE NEWER BIOLOGICAL AND PHYSIOLOGICAL APPROACHES TO CLINICAL PROBLEMS: University of Wisconsin Medical School, Madison, Wis.; William S. Middleton, M.D., F.A.C.P., and Karver L. Puestow, M.D., F.A.C.P., Co-directors; One week, November 16-20. This course will be concluded in the Midwest Regional Meeting of the College at Milwaukee, November 21.
- RHEUMATIC DISEASES: Massachusetts General Hospital, Boston, Mass.; Walter Bauer, M.D., F.A.C.P., Director; One week, date to be determined.

Spring, 1954

Presently it is expected that the Spring, 1954, Schedule will include:

- CLINICAL GASTRO-ENTEROLOGY at New Orleans under Dr. Gordon McHardy.
- ALLERGY at Pittsburgh under Dr. Leo H. Crip.
- ELECTROCARDIOGRAPHY at Detroit under Dr. Gordon Myers.
- HEMATOLOGY at Chicago under Drs. Howard L. Alt, Leon O. Jacobson and L. R. Limarzi.
- INTERNAL MEDICINE at New York under Dr. Franklin M. Hanger.
- INTERNAL MEDICINE at Philadelphia under Dr. Thomas M. Durant.
- NEOPLASTIC DISEASES AND RADIOISOTOPES at New York under Drs. Cornelius P. Rhoads and Rulon Rawson.

FORTHCOMING ACP REGIONAL MEETINGS

Territory	Place of Meeting	Date	Governor
WEST VIRGINIA	White Sulphur Springs	1953 July 24	Paul H. Revercomb, M.D.
NORTH DAKOTA	Fargo	Sept. 12	Robert B. Radl, M.D.
ARKANSAS-OKLAHOMA	Oklahoma City	Sept. 19	A. A. Blair, M.D.
WESTERN NEW YORK	Syracuse	Oct. 9	Wann Langston, M.D.
OHIO	Dayton	Oct. 9	E. C. Reifenshtein, M.D.
MONTANA-WYOMING	Butte	Oct. 9-10	Charles A. Doan, M.D.
SOUTHEASTERN (Cuba, Ala., Fla., Ga., S.C.)	Sea Island, Ga.	Oct. 16-17	Harold W. Gregg, M.D.
NEW ENGLAND (Conn., Maine, Mass., N.H., R.I., Vt.)	Hartford, Conn.	Oct. 28	Carter Smith, M.D., Chmn.
NEW JERSEY	Trenton	Nov. 4	John Leonard, M.D., Chmn.
MIDWEST (Ill., Ind., Iowa, Minn., Wis.)	Milwaukee, Wis.	Nov. 21	Edward C. Klein, Jr., M.D.
NORTH CAROLINA	Chapel Hill	Dec. 3	Karver Puestow, M.D., Chmn.
			Elbert L. Persons, M.D.
		1954	
EASTERN PENNSYLVANIA	Philadelphia	Jan. 15	Thomas McMillan, M.D.
VIRGINIA	(?)	Feb. 25	C. M. Caravati, M.D.
KANSAS	Topeka	March 19	Wm. C. Menninger, M.D.
SOUTHERN ILLINOIS	Peoria	(?)	C. H. Drenckhahn, M.D.

NEW LIFE MEMBERS

The College is pleased to announce that the following Fellows have become Life Members of the American College of Physicians since the publication of the list in last month's issue of this journal:

Dr. Arthur Clayton McCarty, Louisville, Ky.
 Dr. Arthur E. Mahle, Chicago, Ill.
 Dr. Albert Weinstein, Nashville, Tenn.

COMING EXAMINATIONS BY CERTIFYING BOARDS

The American Board of Internal Medicine, William A. Werrell, M.D., Executive Secretary-Treasurer, 1 West Main St., Madison 3, Wis.

Oral Examinations—San Francisco, Calif., Sept. 28, 29, 30, 1953. These dates supersede the originally scheduled dates of Sept. 21, 22, 23.

The American Board of Pediatrics, John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Road, Rosemont, Pa.

Oral Examinations—Ann Arbor, Mich., June 26, 27, 28, 1953.

ANNUAL MEETING, INTERSTATE POSTGRADUATE MEDICAL ASSOCIATION
OF NORTH AMERICA

The 1953 session of the Interstate Postgraduate Medical Association of North America will be held at the Palmer House, Chicago, Nov. 2-5. Further information concerning the program may be obtained from the Association's Managing Director, Arthur G. Sullivan, M.D., 16 North Carol St., Madison, Wis.

INTERAMERICAN FOUNDATION FOR POSTGRADUATE MEDICAL EDUCATION

The Interamerican Foundation for Postgraduate Medical Education has been organized for the purpose of encouraging exchanges of educators, postgraduate students and research workers in the field of medicine and allied sciences in Latin and North American countries. This new Foundation is designed to coördinate and extend these opportunities through a central agency which will, in turn, coördinate its program with that of other groups (private Foundations and governmental agencies) with parallel or overlapping interests in this field. Committees of medical educators in each Latin American country will be asked to assume responsibility for nominating candidates for Fellowships. The proposed program also provides for interchanges of a limited number of visiting lecturers, with expenses defrayed through the Foundation. The Executive Director of the Foundation is Alberto Chattas, M.D., of Cordoba, Argentina, with present headquarters at 112 East Chestnut Street, Chicago 11, Ill.

THE KAPPA DELTA AWARD FOR RESEARCH IN ORTHOPAEDIC SURGERY

A prize of \$1,000, donated by the Kappa Delta Sorority, may be awarded annually by the American Academy of Orthopaedic Surgeons for the best research related to orthopaedic surgery and performed by an American citizen in the United States. The selection will be made from publications after January 1, 1951, or research presented to the Committee on Scientific Investigation of the American Academy of Orthopaedic Surgeons before November 1, 1953.

Researchers interested in competing for the award are requested to secure further information from Dr. John J. Fahey, 1791 West Howard Street, Chicago 26, Ill., Chairman of the Committee on Scientific Investigation of the American Academy of Orthopaedic Surgeons.

DR. HOWARD A. RUSK RECEIVES LASKER AWARD

Dr. Howard A. Rusk, F.A.C.P., New York City, Director of the Institute of Physical Medicine and Rehabilitation of the New York University-Bellevue Medical Center, was recently awarded one of the 1952 Lasker Awards by the American Public Health Association. Dr. Rusk was cited for "distinguished services to humanity through rehabilitation" and for his "achievement in the development of professional training for rehabilitation and for education of the public in the problems of administration of health and medical service."

Dr. Albert M. Snell, F.A.C.P., Palo Alto, Calif., has recently been appointed Chairman of the Veterans Administration's Council of Chief Consultants, the medical advisory group to Vice Admiral Joel T. Boone, (MC), USN (Retired), F.A.C.P., Chief Medical Director, Veterans Administration.

Dr. Herbert W. Rathe, F.A.C.P., Waverly, and Dr. Fred Sternagel, F.A.C.P., West Des Moines, have recently been appointed to the Iowa State Board of Health by Gov. William S. Beardsley. Their terms will expire in January, 1955.

Dr. George R. Herrmann, III, F.A.C.P., Galveston, Tex., was recently awarded an honorary professorship at Santiago, Chile, and was made a member of the Perma Cardiological Society, Lima, Peru, during his lecture tour in South America.

Dr. Edward L. Bortz, F.A.C.P., Philadelphia, a Regent of the College and Past President of the American Medical Association, addressed the First Western Hemisphere Conference of the World Medical Association at Richmond on April 24. Delegates of national medical societies from a score of American nations and guests and participants from 48 states were present. The program was devoted to a review of medical progress and significant fields of medical exploration. Dr. Louis H. Bauer, F.A.C.P., Secretary-General of the World Medical Association, presided at conference sessions and summarized the findings of eleven panel discussions on current medical work. Gov. John S. Battle of Virginia greeted the guests of honor, who, at his invitation, had been appointed by the Governors of the 48 states and the Commissioners of the District of Columbia. As a novel feature, a physician born in 1878 was present from each of the 48 states and the District of Columbia. A commemorative volume, *Seventy-five Years of Medical Progress, 1878-1953*, is to be published with chapters covering the range of medical practice, contributed by participating specialists and practitioners.

Under the Presidency of Dr. Maurice C. Pincoffs, M.A.C.P., Baltimore, the Medical and Chirurgical Faculty of the State of Maryland held its annual meeting in Baltimore, April 28-29. In addition to Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y., retiring President of the American Medical Association, invited guests included Dr. Thaddeus S. Danowski, F.A.C.P., Pittsburgh, who delivered the Harvey Grant Beck Memorial Lecture on "Interrelations of Thyroid and Iodine Metabolism"; Dr. John S. L. Browne, F.A.C.P., Montreal, Can., who gave the I. Ridgeway Trimble Fund Lecture on "The Changing Nature of Medicine"; and Dr. Frank G. MacMurray (Associate), Washington, D. C., who discussed "Cat Scratch Disease." Dr. Pincoffs' Presidential Address was entitled "Thoughts Concerning the Future of Medicine."

Dr. Henry T. Ricketts, F.A.C.P., Chicago, was among the out-of-state speakers at the annual meeting of the Iowa State Medical Society, which was held in Des Moines, April 26-29. He discussed "Diabetes Mellitus in General Practice."

Dr. M. Eugene Flipse (Associate), Miami, addressed the members of the Florida Medical Association when they convened in Hollywood, April 27-29. His paper, "Pheochromocytoma," was discussed by Dr. Walter F. Kvale, F.A.C.P., Rochester, Minn.

Dr. Hugh R. Butt, F.A.C.P., Rochester, Minn., served as moderator for a panel on Clinical and Biochemical Features of Hepatic Insufficiency, which was part of the program of the American Gastro-Enterological Association at its annual meeting in Atlantic City, N. J., May 1-2, under the Presidency of Dr. Albert M. Snell, F.A.C.P., Palo Alto, Calif.

Dr. Jacob Segal, F.A.C.P., Browns Mills, speaking on "Isonicotinic Acid Derivatives on Pulmonary Tuberculosis," addressed the annual meeting of the Medical Society of New Jersey, May 20.

Dr. Eugene B. Ferris, Jr., F.A.C.P., Atlanta, was among the guest speakers at the annual session of the Medical Association of the State of Alabama, held April 16-18 in Birmingham. His presentation was entitled "Evaluation and General Management of Patients with Hypertension."

Dr. Robert C. Hardin, F.A.C.P., Iowa City, addressed the St. Joseph (Mo.) Clinical Society, April 9, his topic being "Blood Transfusions."

Dr. Thomas M. Durant, F.A.C.P., and Dr. W. Edward Chamberlain, F.A.C.P., Philadelphia, delivered six of the Sommer Memorial Lectures in Portland, Ore., April 22-24. Dr. Durant discussed "Congestive Failure: Pathophysiology and Management of Resistant Cases"; "Cardiac Arrhythmias: Recognition and Management"; and "Coronary Disease: Etiology and Management." Dr. Chamberlain's presentations were on "What the General Practitioner Should Know About the Biological Effects of Irradiation," "Low Back Pain," and "General Considerations in the Treatment of Cancer." The lectures were part of the joint annual meeting of the Alumni Association of the University of Oregon Medical School and the Oregon Chapter of the American Academy of General Practice.

Under the Presidency of Dr. Truman C. Terrell, F.A.C.P., Fort Worth, the Centennial Anniversary Session of the Texas Medical Association was held in the Shamrock Hotel, Houston, April 26-29. Guest speakers and their subjects included Dr. Francis F. Rosenbaum, F.A.C.P., Milwaukee, "Recognition and Management of Paroxysmal Rapid Heart Action"; Dr. George E. Burch, Jr., F.A.C.P., New Orleans, who addressed the Texas Heart Association, "Management of Angina Pectoris"; and Dr. Stewart G. Wolf, Jr., F.A.C.P., Oklahoma City, "Practical Considerations in the Physiology of Pain with Special Reference to Treatment."

Dr. H. Russell Fisher, F.A.C.P., Los Angeles, was one of the invited speakers at the annual meeting of the American Laryngological Association, which convened in New Orleans, April 26-27, under the Presidency of Dr. Louis H. Clerf, F.A.C.P., Philadelphia.

Dr. Samuel P. Asper, Jr. (Associate), Baltimore, was among the guest speakers who discussed "Radioisotopes and Their Use in Diagnosis and Treatment" at the annual session of the American Association for the Study of Neoplastic Diseases, which met in Baltimore, April 30-May 2. Dr. Elbert DeCoursey, F.A.C.P., Washington, D. C., addressed the dinner meeting.

The annual meeting of the American Association of Railway Surgeons was held in Chicago, April 7-9. Speakers and their topics, all from the Chicago area, included Dr. Lowell D. Snorf, Sr., F.A.C.P., "Massive Upper Gastrointestinal Hemorrhage"; Dr. Walter L. Palmer, F.A.C.P., College Regent, and Dr. Joseph B. Kirsner, F.A.C.P., "Antisecretory Drugs in the Treatment of Peptic Ulcer"; Dr. Harley E. Cluxton, Jr. (Associate), "Some Practical Uses of Hormones"; Dr. Chauncey C. Maher, Sr., F.A.C.P., "Evaluation of the Cardiac Patient for Surgery"; and Dr. Eugene L. Walsh, F.A.C.P., "Treatment of Early Pulmonary Tuberculosis as Disclosed by Mass X-Ray Survey."

Dr. Cecil J. Watson, F.A.C.P., Minneapolis (Porphyrins), Dr. William Dame-shek, F.A.C.P., Boston (Iron and Hemoglobin in Leukemias), and Dr. Carl V. Moore, F.A.C.P., St. Louis, College Governor for Missouri (Iron Metabolism), are listed on the program of the Fourth Congress of the European Society of Haematology, which will meet in Amsterdam, Sept. 8-12.

Dr. Virgil P. Sydenstricker, M.A.C.P., Augusta, Ga., last month participated in a seminar conducted at the University of Edinburgh, Scotland.

Dr. Charles M. Caravati, F.A.C.P., Richmond, College Governor for Virginia, participated in the Sixth Annual Medical Symposium in the Greensboro (N. C.) Academy of Medicine, March 25. The title of his paper was "Lesions of the Distal Stomach."

Under the Presidency of Dr. J. Warrick Thomas, F.A.C.P., Richmond, Va., the American College of Allergists held its annual congress in Chicago, April 27-29. Dr. Hyman Miller (Associate), Beverly Hills, Calif., acted as moderator of a clinical panel on Psychosomatic Allergy; and Dr. M. Murray Peshkin, F.A.C.P., New York, newly installed President, summarized the findings from four seminars on "Emotional Factors in Allergic Disorders" and the answers to a questionnaire, "How Do You Feel About Feelings?" Dr. Ralph H. Kunstadter, F.A.C.P., Chicago, participated in a round-table luncheon discussion on Pediatric Allergy; and Dr. Walter S. Burrage, F.A.C.P., Boston, presented a paper on "Microscopic Observations of the Intrahepatic Circulation of Living Guinea Pigs Before and During Anaphylaxis."

Dr. David T. Smith, F.A.C.P., Durham, N. C., former President of the National Tuberculosis Association, reported on "An Explanation of the Apical Localization of Reinfection Tuberculosis" at the joint annual meeting of the Colorado Tuberculosis Association and the Colorado Trudeau Society. The meeting was held in Denver, April 17-18, and Dr. Smith also addressed the dinner meeting on "New Concepts and Methods for the Control and Elimination of Tuberculosis."

Among the guest speakers and their topics at the annual session of the Indiana Academy of General Practice, held in Indianapolis, April 15-16, were Dr. Joseph F. Ross, F.A.C.P., Boston, "Hematology and the General Practitioner"; Dr. Garfield G. Duncan, F.A.C.P., Philadelphia, "Management of Diabetes During Acute Complications"; and Dr. Harry L. Smith, F.A.C.P., Rochester, Minn., "Movement of the Heart Valves and Cardiac Sounds."

Dr. George W. Thorn, F.A.C.P., Boston, delivered the Dr. Jack W. Kolson Memorial Lecture, sponsored by the House Staff of Sinai Hospital of Baltimore, at Johns Hopkins Hospital, April 17. His subject was "Studies of the Adrenal Cortex."

Dr. Charles W. Hock (Associate), Augusta, Ga., spoke on "Melena and Hematemesis of the Upper Intestinal Tract" at Salisbury, N. C., April 15. His paper was part of the annual General Practice Symposium sponsored by the Rowan Davie County Chapter of the American Academy of General Practice.

Dr. Oscar C. E. Hansen-Pruss, F.A.C.P., Durham, Professor of Medicine at Duke University School of Medicine and Chief of Allergy and Hematology Services at Duke Hospital, was one of the two speakers to address the Tennessee Academy of General Practice on April 15. The session was held in Nashville in connection with the yearly meeting of the Tennessee State Medical Association.

Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y., was the guest speaker at the annual dinner meeting of the Tufts Medical Alumni Association, held April 15 in Boston. His address concerned "The American Medical Association and the Problems Facing Medicine." Dr. Joseph M. Hayman, Jr., F.A.C.P., Dean of the School, also addressed the alumni gathering.

Dr. George E. Burch, Jr., F.A.C.P., New Orleans; Dr. Samuel F. Haines, F.A.C.P., Rochester, Minn., and Dr. John B. Youmans, F.A.C.P., Nashville, Tenn., were among the guest speakers at the annual meeting of the Arkansas Medical Society, held April 20-22 in Little Rock.

Dr. Albert Weinstein, F.A.C.P., Nashville, Tenn., and Dr. Claude-Starr Wright (Associate), Columbus, Ohio, were two of the out-of-state speakers at the annual convention of the Kentucky Chapter of the American Academy of General Practice. The theme of the meeting, which was held in Louisville, April 22-23, was "Recent Advances in Medicine as They Will Apply to General Practice."

At the yearly meeting of the Ohio State Medical Association, held in Cincinnati, April 21-23, Dr. Joseph B. Kirsner, F.A.C.P., and Dr. Lester R. Dragstedt, F.A.C.P., Chicago, discussed, respectively, the medical and surgical aspects of the management of peptic ulcer; and Dr. Charles K. Friedberg, F.A.C.P., New York, presented a paper on "Treatment of Coronary Heart Disease."

Dr. Carl V. Moore, F.A.C.P., St. Louis, was the banquet speaker at the anniversary dinner of the foundation of the Minneapolis Society of Internal Medicine, held in the Minneapolis Club, Feb. 18. His topic was "Newer Concepts of Thrombocytopenic Purpura."

Dr. Albert H. Rowe, F.A.C.P., San Francisco, delivered a lecture on "The Challenge of Food Allergy in Medical Practice" before the New Jersey Academy of Medicine in Newark on Feb. 17.

Guest speakers at the Hartford (Conn.) Hospital, where lectures and demonstrations were held every Saturday from April 4-June 13, have included the following members of the College: Dr. Arthur J. Geiger, F.A.C.P., New Haven, "Idiopathic Pleuro-pericarditis (and its differentiation from coronary occlusion)"; Dr. Giles F. Filley (Associate), Trudeau, N. Y., "Medical and Surgical Aspects of Pulmonary Function Studies"; Dr. Dorothy M. Horstmann (Associate), New Haven, "Recent Advances in Poliomyelitis"; George A. Wolf, Jr., F.A.C.P., Burlington, Vt., "Dyspnea"; and Dr. Chester S. Keefer, F.A.C.P., Boston, College Regent, a case presentation.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., recently spoke at the new medical school and hospital of the University of North Carolina, Chapel Hill, on "Some Clinical and Historical Aspects of Diseases of the Pancreas."

Capt. Julian Love, (MC), USN, formerly Chief of Medicine at the U. S. Naval Hospital at Philadelphia, and more recently Commanding Officer of the U. S. Naval Hospital at Oakland, Calif., has been appointed Commanding Officer of the U. S. Naval Hospital at Corona, Calif., to assume duties on or about July 15, 1953.

Dr. Lewis Gunther, F.A.C.P., Beverly Hills, Calif., was appointed Chief of Medicine at the Cedars of Lebanon Hospital on Jan. 1, succeeding the late Dr. Morris Henry Nathanson, F.A.C.P.

Dr. Louis Ochs, Jr., F.A.C.P., New Orleans, Clinical Assistant Professor of Medicine at Louisiana State University School of Medicine, has recently been appointed Chief of Gastro-enterology at Touro Infirmary.

Dr. Harold H. Golz, F.A.C.P., former Chief of the Medical Service and Chief of Staff for the Arabian American Oil Company in Saudi Arabia, has recently been appointed Assistant Medical Director of the American Cyanamid Company.

Dr. E. Gurney Clark, F.A.C.P., New York City, has been named Medical Consultant to the American Social Hygiene Association. Dr. Clark has recently been Visiting Professor in the Department of Dermatology and Syphilology at the University of Oslo School of Medicine in Norway.

Dr. Cornelius H. Traeger, F.A.C.P., New York City, recently resigned as Medical Director of the National Multiple Sclerosis Society; he will, however, serve as Consultant Medical Director.

Dr. James L. McCartney, F.A.C.P., Garden City, N. Y., author of *The Drama of Sex*, had a novel, *Frustrated Martyr*, published April 23 by Exposition Press. This historical narrative covers the period 1890-1922 in China. The story is based on the life of his father, who started the first hospital in Chungking and practiced in that city until his death in 1928.

Dr. Jerome G. Kaufman, F.A.C.P., Newark, N. J., has recently been elected a member of the Board of Directors of the American Heart Association.

Dr. Howard R. Bierman, F.A.C.P., San Francisco, spoke on "The Balance Concept of Leukemia in Man" at the Montefiore Hospital for Chronic Diseases, New York City. The lecture, delivered May 1, was sponsored by the Hospital's Division of Neoplastic Diseases.

Dr. Chester M. Jones, F.A.C.P., Boston, delivered the Annual Clarence M. Jackson Lecture on "Gastrointestinal Symptoms with Particular Reference to Motor Disturbances" at the University of Minnesota, Minneapolis, April 28.

Dr. Alexander B. Gutman, F.A.C.P., New York, delivered a lecture on "Recent Advances of Purine Metabolism and Their Relationship to the Pathogenesis of Gout" at the Boston University School of Medicine, April 27. The lecture was sponsored by the University's chapter of Alpha Omega Alpha fraternity.

Dr. Cotter Hirschberg (Associate), Topeka, Kans., speaking on "Emotional Problems of Childhood: Their Management in General Practice," addressed the annual meeting of the Missouri State Medical Association, held in Kansas City, April 26-29.

Dr. Samuel M. Feinberg, F.A.C.P., Chicago, and Dr. Travis W. Winsor, F.A.C.P., Los Angeles, were among the out-of-state speakers at the annual meeting of the Arizona Medical Association, which was held April 26-29 in Tucson. Their respective subjects were "Role of the Nonspecialist in the Care of Allergic Diseases" and "Management of Peripheral Arterial Occlusive Disease." Dr. Feinberg also addressed the Arizona Society of Allergy.

Dr. William S. Middleton, M.A.C.P., Dean of the University of Wisconsin School of Medicine, Madison, and Dr. Dwight L. Wilbur, F.A.C.P., College Regent, Clinical Professor of Medicine at Stanford University School of Medicine, San Francisco, have recently been appointed to the Civilian Health and Medical Advisory Council. The Council supplants the former Armed Forces Medical Policy Council and will advise Dr. Melvin A. Casberg, newly appointed Assistant to the Secretary of Defense, on "all health and medical policies, plans, standards and criteria" that he "deems appropriate and necessary."

Dr. George E. Burch, Jr., F.A.C.P., New Orleans, Professor and Chairman of the Department of Medicine at Tulane University School of Medicine, was recently selected by *Modern Medicine* as one of ten outstanding recent contributors to medical knowledge.

The March, 1953, issue of *Archives of Internal Medicine* cited Dr. Joseph Hersey Pratt, F.A.C.P., Boston, Emeritus Professor of Medicine at Tufts College Medical School, on attaining his eightieth birthday, Dec. 5, 1952. The author of approximately 150 medical publications, Dr. Pratt pioneered the use of prolonged bed rest in the treatment of pulmonary tuberculosis and was among the first to introduce group therapy in the practice of medicine.

Dr. Kenneth M. Lynch, F.A.C.P., Charleston, was honored at the Founder's Day Banquet when his associates and former students presented his portrait to the Medical College of South Carolina. Dr. Lynch, President of the College, formerly was Professor of Pathology and Dean of the medical school from 1943 until 1948.

A portrait of the late Dr. N. Barnwell Heyward (Associate), Columbia, S. C., was recently unveiled in the Lily Hardin Nurses Home of the South Carolina Baptist Hospital, where Dr. Heyward had been a staff member for many years. He had also been Secretary of the South Carolina Medical Association and of the South Carolina State Board of Medical Examiners.

Dr. Robert M. Kark, F.A.C.P., Professor of Medicine at the University of Illinois College of Medicine, Chicago, has been elected a Fellow of the Royal College of Physicians of London, England.

Dr. Rudolph H. Kampmeier, F.A.C.P., Nashville, Tenn., was promoted Jan. 1 to Professor of Medicine at Vanderbilt University School of Medicine.

Dr. Morris Shushan (Associate), New Orleans, has recently been appointed Clinical Associate Professor of Medicine at Louisiana State University School of Medicine.

At the annual meeting of the Texas Diabetes Association in Houston, April 26, the following officers were elected: President—Dr. Raymond L. Gregory, F.A.C.P., Galveston; First Vice President—Dr. George M. Jones, F.A.C.P., Dallas; Second Vice President—Dr. L. B. Reppert (Associate), San Antonio; Secretary-Treasurer—Dr. Edmond K. Doak, F.A.C.P., Houston. Among the Councilors chosen were: Dr. Ralph G. Greenlee, F.A.C.P., Temple; Dr. James A. Greene, F.A.C.P., Houston; and Dr. Edwin L. Rippy, F.A.C.P., Dallas.

OBITUARIES

DR. CYRUS J. CLARK

Dr. Cyrus J. Clark, F.A.C.P., was born at Carmel, Ind., on November 16, 1900, and met his tragic and untimely death on January 22, 1953, as a result of an automobile accident.

He attended Indiana University, where he obtained his B.S. degree in 1921 and his M.D. degree in 1923. He served an internship at the Indianapolis General Hospital and almost immediately began his career as a teacher by associating himself with the Heart Clinic, which had only recently been established and in which he maintained a very active interest until his death. He accepted and discharged with merit many other teaching obligations in the School of Medicine. Thus he was Assistant Professor of Medicine in 1935, Associate Professor, Department of Cardiovascular Diseases, Clinical Professor of Cardiology and Chairman of the Department of Economics and Postgraduate Education. 1925 found him as a visiting staff member of Indianapolis General Hospital, and Co-chief of the Heart Clinic in 1932; later, Dr. Clark became Chief of Medical Staff and Chief of Vascular Disease Clinics. He was a member of the visiting staff, Methodist and St. Vincent's Hospitals, and Medical Consultant, Sunnyside Sanatorium.

In addition he always had strong ideals of medicine and fearlessly worked for them; as a result, he became very active in organized medicine. By 1933 he was Secretary of the Medical Section of the State Medical Association, and the next year its Chairman. In this latter capacity he also served as Chairman of the Committee on Graduate Education, a position held until 1938. From 1936 to 1944 Dr. Clark was Council Member from the Seventh Medical District, and in 1947-1948 he headed a committee which screened applicants for medical school scholarships. In the Heart Foundation he became a member of the Board of Trustees. He was elected to the Executive Committee of the State Association, 1950, and made its Chairman, 1951. He was active on a committee which established the Blue Shield Plan throughout the state. He was a Diplomate of the American Board of Internal Medicine (1936) and a Fellow of the American College of Physicians (1937), in which he maintained an abiding interest.

Dr. Clark was Colonel (MC) in the Thirty-second General Hospital, sponsored by Indiana University, and became its Commanding Officer, a position he filled with distinction.

He was a member of Phi Gamma Delta, Phi Ro Sigma and Alpha Omega Alpha fraternities. When the Veterans Hospital became affiliated with the Medical School, he became the Senior Consultant. He had an uncanny capacity to get things done.

As a man "Cy," as his friends knew him, was generous, loyal and sincere. He loved to entertain. He had enthusiastic interests in outdoor sports. As a raconteur there were few his equal.

He was uncompromising in his ideals as related to the practice of medicine. He was a devoted husband and father. Surviving him are his wife, Mrs. Edith Clark, two sons, Eric and Cyrus III, and a daughter Patricia.

The American College of Physicians has lost a most active Fellow; the medical profession as a whole, a real friend; his close friends, a boon companion; and his patients, a devoted counselor. His name will be long remembered.

JAMES O. RITCHEY, M.D., F.A.C.P.,
Governor for Indiana

DR. RICHARD F. HERNDON

Dr. Richard Fleetwood Herndon, F.A.C.P., was born in Springfield, Ill., on January 11, 1890, and died after an extended illness on February 19, 1953, at his home in Springfield.

In 1911 Dr. Herndon completed his undergraduate education, receiving an A.B. degree from the University of Illinois and a B.S. degree from the University of Chicago. He received his M.D. degree from Rush Medical College in 1914, interned at Cook County Hospital and the Chicago Institute of Infectious Diseases, 1914-16. He then became affiliated with the Patton-Evans Clinic of Springfield, continuing as a member of this group until 1939 when he organized the Springfield Clinic, in which he served as Chief of the Department of Medicine until ill health forced his retirement.

Dr. Herndon was an aggressive medical observer and, as a result, contributed to the medical literature on numerous occasions by way of monographs and shorter articles. In 1946 he was author of the book *An Introduction to Essential Hypertension*.

He participated actively in various medical organizations. In 1943 he was President of the Sangamon County Medical Society. He was a member of the Chicago Society of Internal Medicine, a Diplomate of the American Board of Internal Medicine, and had been a Fellow of the American College of Physicians since 1942.

Dr. Herndon is survived by his wife and four children, one of whom is now serving as a physician with the American forces in Korea.

CHARLES H. DRENCKHAHN, M.D., F.A.C.P.,
Governor for Southern Illinois

DR. PAUL J. LEWIS

Dr. Paul John Lewis, F.A.C.P., died in Yakima, Wash., Dec. 20, 1952, where he had practiced internal medicine since 1921. He had suffered a stroke in 1950, which had caused him to give up his practice at that time.

Dr. Lewis was born in Wisconsin, Oct. 7, 1888, and attended Platteville State Normal School and the University of Wisconsin. Before receiving his degree of Doctor of Medicine from Northwestern University Medical School in 1915, he had been Instructor in Science and Assistant Principal of Sharon and Oconomowoc High Schools. Dr. Lewis spent his internship and residency at St. Luke's Hospital, and in 1921 became affiliated with the St. Elizabeth Hospital, Yakima, where he was later Instructor of Nurses for four years. From 1924 until 1950 he had also been Internist at the Yakima Medical and Surgical Clinic. During World War I, Dr. Lewis served in the Medical Corps of the U. S. Army as Commanding Officer of a Field Hospital Company.

He was a former President of the Yakima County Medical Society and was a member of the Washington State Medical Association, the American Medical Association, the North Pacific Society of Internal Medicine, the American Trudeau Society and the American Heart Association. A Diplomate of the American Board of Internal Medicine, he became a Fellow of the American College of Physicians in 1935.

Dr. Lewis, who was held in high esteem, has been greatly missed since he was forced to give up his practice, not only by his patients and friends in Yakima, but throughout the state as well.

GEORGE H. ANDERSON, M.D., F.A.C.P.,
Governor for Washington

DR. OSCAR LOTZ

Oscar Lotz, M.D., F.A.C.P., Wisconsin leader of the crusade against tuberculosis, died from metastatic pulmonary carcinomatosis of undetermined origin on January 15, 1953.

Dr. Lotz was born in Milwaukee, Wis., on June 23, 1880. In 1902 he received a Certificate of Proficiency in Biology from the University of Pennsylvania. In 1905 he received his M.D. degree from the University of Pennsylvania School of Medicine.

After an internship at Mercy Hospital, Pittsburgh, and a residency at Johnston Emergency Hospital, Milwaukee, he began practice in Milwaukee in 1907. He was Attending Physician at Milwaukee Maternity Hospital from 1908 to 1910. Later he became a member of the staff of Columbia Hospital, Milwaukee, and Consultant to Milwaukee Children's Hospital.

Dr. Lotz's greatest opportunity for service began when he joined the staff of the Wisconsin Anti-Tuberculosis Association in 1917, with which he was associated until his death. He first served as Medical Adviser of the Association, then as its Executive Secretary from 1939 to 1951, and finally as Executive Consultant. During his years as executive head of the Association, grants were made to both medical schools in the state for research and teaching, rehabilitation services to sanatoria were instituted, aid to help education in schools was fostered, Come-Back clubs for recovered patients were organized, and graduate courses for practicing physicians were given. Likewise his Association became the first one to put a chest x-ray bus on the highway. Dr. Lotz helped to urge the adoption by the state of a model law for the free hospital care of the tuberculous. In brief, he attacked the problem of tuberculosis from every angle. He had been Consultant to Lake View Sanatorium since 1919, Rocky Knoll since 1926, Sunny View since 1929, and Maple Crest and River View since 1935, all of Wisconsin.

From 1910 to 1912 Dr. Lotz was an Instructor in Pharmacology at the Wisconsin College of Physicians and Surgeons in Milwaukee. He then became Instructor in Physical Diagnosis at Marquette University School of Medicine from 1914 to 1916. In addition, from 1931 until 1946, Dr. Lotz served on the extra-mural faculty of the University of Wisconsin Medical School as an Associate Preceptor. In 1925 he became a member of the Bureau of Nursing Education. He was a member of the Wisconsin State Board of Medical Examiners from 1918 to 1924 and was President of the Board in 1922.

During World War I he was a member of the Board of Review for draft rejectees. In 1918 he was Chairman of the Committee on Health of the Milwaukee County Council of Defense. He was on the Board of Directors of the Wisconsin Society for Mental Hygiene and the Wisconsin Heart Association. He was a Wisconsin representative on the Advisory Board of the American Trudeau Society. In 1943 he was Vice President of the Mississippi Valley Trudeau Society, and in 1948-49 he was President of the Mississippi Valley Conference on Tuberculosis. In 1918 he became the First Vice President of the Wisconsin State Medical Society. He was a long-time Secretary of the Milwaukee Academy of Medicine, of which he was President in 1923. He was a founding member of the Internist Club of Milwaukee. He held memberships in the Milwaukee County Medical Society, the National Tuberculosis Association, and the American Trudeau Society, in addition to being a Fellow of the American Medical Association. In 1949 he was presented with the "Salute of the Year" by the Milwaukee Come-Back Club, and in 1944 given an Award of Merit by the Milwaukee Vocational School of Nursing in recognition of 11 years of service as a Lecturer in Tuberculosis.

Dr. Lotz became a Fellow of the American College of Physicians in 1928 and later a Diplomate of the American Board of Internal Medicine.

KARVER L. PUESTOW, M.D., F.A.C.P.,

Governor for Wisconsin

DR. ROBERT H. McCONNELL

Dr. Robert Hall McConnell, a Fellow of the American College of Physicians since 1939, died in New York City on December 21, 1952, of arteriosclerotic heart disease.

He was born in Passaic, N. J., December 25, 1873; he attended the College of the City of New York and received his degree of Doctor of Medicine from Columbia University College of Physicians and Surgeons in 1895. He served as an Interne in the Lebanon and Roosevelt Hospitals from 1895 until 1897 and for the following two years was Clinical Assistant in the Vanderbilt Clinic. Dr. McConnell was Attending Physician and later Medical Director of the French Hospital, and was Director of the First Medical Division of that hospital beginning in 1909. He became Consulting Physician at the Yonkers Professional Hospital in 1938, and was formerly Consultant to the East Side Clinic and the N.V.A. Sanatorium in Saranac.

During the First World War, Dr. McConnell served with the rank of Major (MC), U. S. A., as Chief of Service of Base Hospital 150, and later as Chief of Base Hospital 38 in White Plains. He received numerous French decorations, including Officer of Public Instruction and Officer of the Legion of Honor. He was a Major in the Seventh Regiment of the New York National Guard. Dr. McConnell had been a member of the New York Academy of Medicine, the Medical Society of the State of New York and the American Medical Association.

His friends and medical colleagues note with deep regret the passing of Dr. McConnell at this time.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

DR. GEORGE L. STEELE

Dr. George Louis Steele, F.A.C.P., of Springfield, Mass., died on Feb. 14, 1953. He had had an attack of coronary thrombosis in 1939 but continued to work until several weeks before his death. He was born in Springfield on February 24, 1891, and graduated with honors from the University of Vermont College of Medicine in 1914, where he was President of his class. He served as an Interne at the Springfield Hospital in 1916 and subsequently became Senior Resident Physician of the Essex County (N. J.) Sanatorium. He did postgraduate work at Harvard Postgraduate Medical School.

At the time of his death, Dr. Steele was Cardiologist at the Springfield Municipal Hospital and Consultant and Cardiologist at the Mary Lane Hospital, Ware. He had also served as Consultant and Cardiologist at the Wesson Memorial Hospital, the Springfield Isolation Hospital, the Shriners Hospital for Crippled Children, Noble Hospital, Westfield, Cooley Dickinson Hospital, Northampton, and Wing Memorial Hospital, Palmer.

He was a past President of the Springfield Municipal Hospital Staff, Hampden District Medical Society and the Springfield Academy of Medicine. Dr. Steele became a Fellow of the American College of Physicians in 1929 and a Diplomate of the American Board of Internal Medicine in 1937. During World War II, he was a member of Medical Advisory Board No. 3 of the Massachusetts Selective Service System. In 1947 he became a member of the Board of Trustees of the Springfield Municipal Hospital and in 1951 he was elected President of the Western Chapter of the Massachusetts Heart Association.

He is survived by his wife and two children. It is with sincere regret that Dr. Steele's many friends and confreres record his passing at this time.

JAMES Z. NAURISON, M.D., F.A.C.P.

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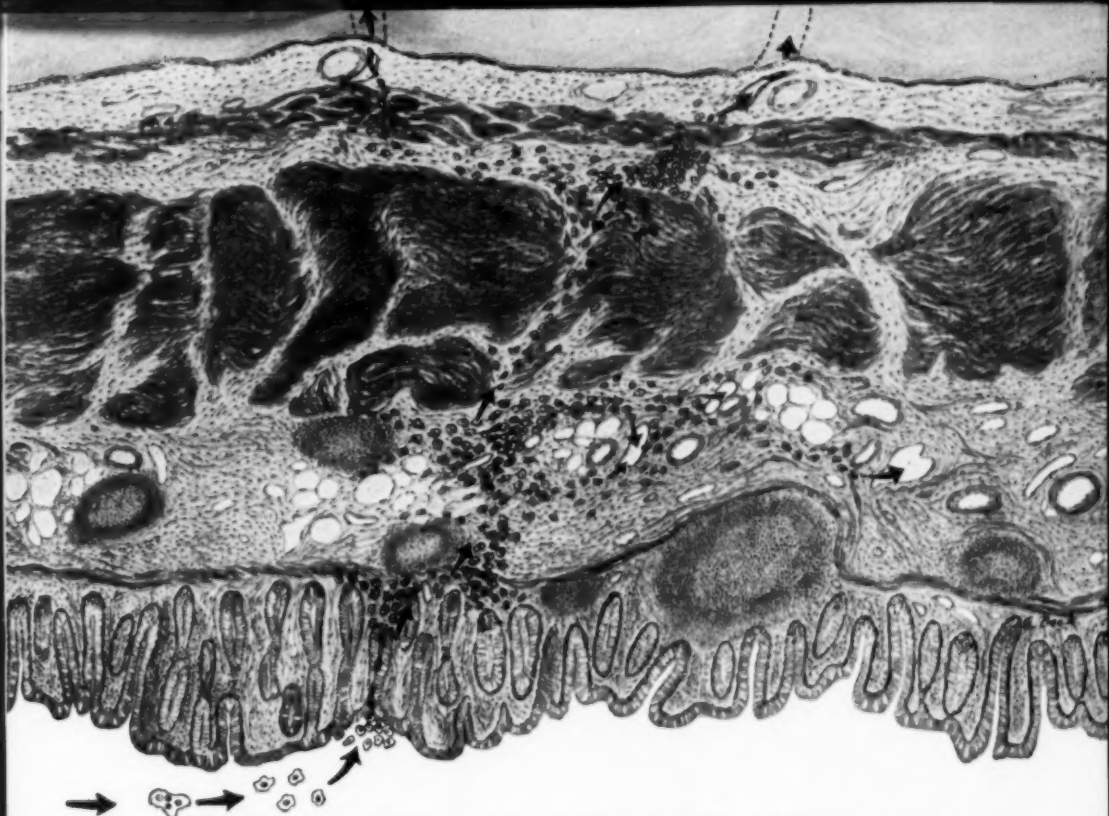
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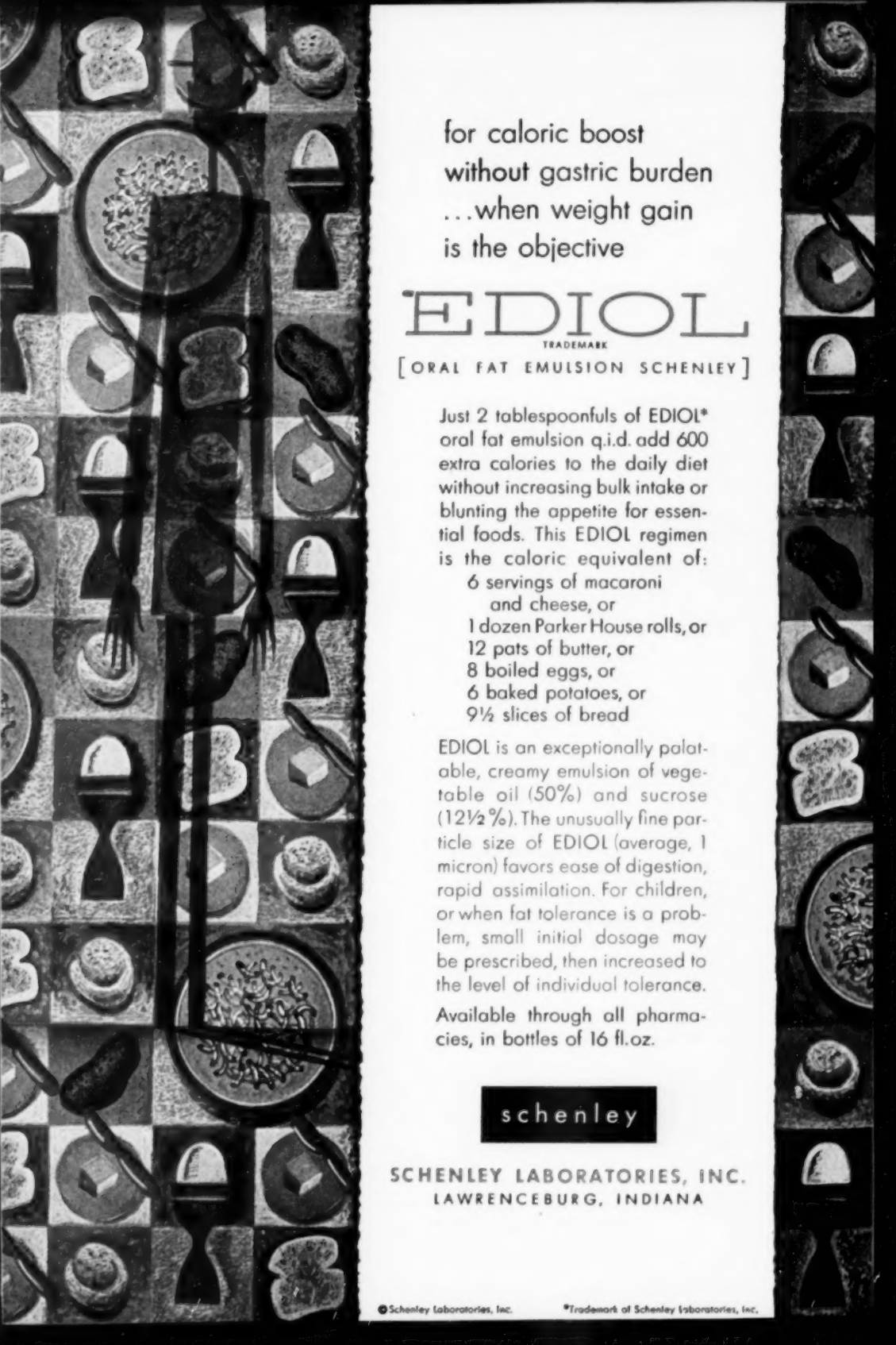
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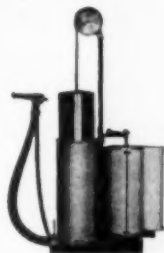


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